The European Agency for the Evaluation of Medicinal Products

London, 27 July 2000
CPMP/1390/00

CPMP ASSESSMENT REPORT

LUVERIS

International Non-proprietary Name: lutropin alfa

Procedure No. EMEA/H/C/292/00/00

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PRODUCT INFORMATION

Name of the medicinal product:	Luveris 75 IU
Marketing Authorisation Holder:	Ares-Serono (Europe) Ltd. 24, Gilbert Street London W1Y 1RJ United Kingdom
Active substance:	recombinant human luteinising hormone (r-hLH)
International Nonproprietary Name:	lutropin alfa
Pharmaco-therapeutic group (ATC Code):	Gonadotrophins G03G
Therapeutic indication:	Luveris in association with a follicle stimulating hormone (FSH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L.
Pharmaceutical form:	Powder and solvent for solution for injection
Strength:	75 IU
Route of administration:	Subcutaneous use
Packaging:	Powder: vials Solvent: vials or ampoules
Package sizes:	1 vial of powder + 1 ampoule or vial of solvent 3 vials of powder + 3 ampoules or vials of solvent 10 vials of powder + 10 ampoules or vials of solvent

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N.B. The abstract and the SPC, package leaflet and labelling texts relating to the CPMP opinion are available in all official languages of the European Union.

I. BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Ares-Serono (Europe) Ltd. submitted on 01 June 1999 an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) for Luveris 75 IU, in accordance with the centralised procedure falling within the scope of Part A of the Annex to Council Regulation No (EEC) 2309/93 of 22 July 1993, as amended.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

2. Steps taken for the assessment of the product

- The procedure started on 25 June 1999
- The Rapporteur's first assessment report was circulated to all CPMP Members on 13 September 1999. The Co-Rapporteur's first assessment report was circulated to all CPMP Members on 6 September 1999.
- The Rapporteur's and Co-Rapporteur's draft list of question was circulated to all CPMP Members on 13 October 1999.
- During the meeting on 19-21 October 1999 the CPMP agreed on the consolidated list of questions to be sent to the company. The final consolidated list of questions was sent to the company on 21 October 1999.
- The company submitted the responses to the consolidated list of questions on 3 April 2000
- The Rapporteur and Co-Rapporteur circulated the response assessment report on the company's responses to the list of questions to all CPMP Members on 18 May 2000.
- During the June 2000 plenary meeting the CPMP agreed on the list of outstanding issues to be sent to the company.
- The company submitted the responses regarding the outstanding issues on 28 June 2000.
- During the meeting on 25-27 July 2000 the CPMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Luveris 75 IU on 27 July 2000.

II. GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing Authorisation Holder

Manufacturer of the active substance

Laboratoires Serono S.A.
1170 Aubonne
Switzerland
Manufacturing Authorisation issued on 1 January 1999 by the Département de la Santé et de l'action sociale (Department of Interior and of Public Health), Canton de Vaud, Switzerland.

Manufacturers of the finished product

Luveris 75 IU (powder)
Laboratoires Serono S.A.
1170 Aubonne
Switzerland
Manufacturing Authorisation issued on 1 January 1999 by the Département de la Santé et de l'action sociale (Department of Interior and of Public Health), Canton de Vaud, Switzerland.

Solvent (ampoules)
Pharma Hameln GmbH
31789 Hameln
Germany
Manufacturing Authorisation issued on 26 March 1996 by the Bezirksregierung Hannover (District Government of Hannover), Hannover, Germany.

Solvent (vials)
Gensia Sicor Pharmaceuticals Inc.
Irvine CA 92618-1902
U.S.A.
Manufacturing Authorisation issued on 25 March 1998 by the Department of Health Services, Food and Drug Branch, State of California, USA

Manufacturer responsible for batch release

Industria Farmaceutica Serono S.p.A.
70123 Bari
Italy
Manufacturing Authorisation issued on 7 October 1999 by the Ministero della Sanità (Italian Ministry of Health), Rome, Italy.

2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

III. SCIENTIFIC DISCUSSION

1. Introduction

Lutropin alfa, the active ingredient in Luveris, is a recombinant human luteinising hormone (r-hLH) produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary (CHO) cells. Luteinising hormone (LH) is a heterodimeric glycoprotein that is secreted by the anterior pituitary gland and, in conjunction with other reproductive hormones, is important in the regulation of follicular development and ovulation in women.
Luveris in association with a follicle stimulating hormone (FSH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency as defined by an endogenous serum LH level < 1.2 IU/l, i.e. to induce ovulation in anovulatory women with hypogonadotrophic hypogonadism (HH) (WHO Group I anovulation). In LH and FSH deficient women, the objective of Luveris therapy in association with follitropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of human Chorionic Gonadotrophin (hCG).

Current treatment of severe HH consists of urine derived human menopausal gonadotrophins (h-MG) since the patients need both FSH and LH. Follicular development can be achieved with FSH alone, but inadequate follicular oestradiol production may lead to impaired endometrial growth and failure to form a functional corpus luteum when exposed to hCG. The production of these gonadotrophins extracted from urine involves the collection and processing of large amounts of urine from post-menopausal women. Another approved treatment consists of gonadotrophin releasing hormone (GnRH) that stimulates endogenous FSH and LH secretion when administered every 60 to 120 minutes over a week via a portable pump. However, such treatment requires a normal pituitary function.

Luveris is intended for daily subcutaneous administration simultaneously with follitropin alfa. Treatment should be tailored to the individual patient's response as assessed by measuring (i) follicle size by ultrasound and (ii) oestrogen response. A recommended regimen commences at 75 IU of lutropin alfa (ie. one vial of Luveris) daily associated with 75-150 IU FSH.
If an FSH dose increase is deemed appropriate, dose adaptation should preferably be performed at 7-14-day interval and preferably by 37.5-75 IU increments. The treatment may be extended for up to 5 weeks.

When an optimal response is obtained, a single injection of 5,000 IU to 10,000 IU hCG should be administered 24-48 hours after the last Luveris and FSH injections. The patient is recommended to have coitus on the day of, and on the day following, hCG administration. Alternatively, intrauterine insemination (IUI) may be performed. Luteal phase support may be considered since lack of substances with luteotropic activity (LH/hCG) after ovulation may lead to premature failure of the corpus luteum.
If an excessive response is obtained, treatment should be stopped and hCG withheld. Treatment should recommence in the next cycle at a dose of FSH lower than that of the previous cycle.

List of abbreviations

AEs	: adverse events
AUC	: area under the curve
B.P.	: British Pharmacopoeia
CHO	: chinese hamster ovary
ELISA	: enzyme-linked immunosorbent assay
EPDB	: extended population doubling banks
FBS	: foetal bovine serum
FSH	: follicle stimulating hormone
GMP	: Good Manufacturing Practice
GnRH	: gonadotrophin releasing hormone
HCG	: chorionic gonadotrophin
HH	: hypogonadotrophic hypogonadism
h-MG	: human menopausal gonadotrophins

IM	: intravenous, muscular
IUI	: intrauterine insemination
IV	: intravenous
LH	: luteinising hormone
MCB	: master cell bank
OHSS	: ovarian hyperstimulation syndrome
p-hLH	: pituitary human LH
r-hFSH	: recombininant human FSH
r-hLH	: recombinant human luteinising hormone (r-hLH)
RP-HPLC	: reversed phase high performance liquid chromatography
SC	: subcutaneous
SDS-PAGE	: sodium dodecyl sulphate polyacrylamide gel electrophoresis
SE-HPLC	: side exclusion high performance liquid chromatography
TSH	: thyroid stimulating hormone
u-hLH	: urinary human LH
USP	: United States Pharmacopoeia
WCB	: working cell banks

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Luveris is a sterile and freeze-dried powder for solution for subcutaneous injection presented in glass vials with rubber stoppers. Luveris is available in one dosage strength: 75 IU per vial of lutropin alfa (equivalent to 3.4 micrograms). The powder is to be reconstituted with the accompanying solvent (1.0 ml water for injections) presented either in ampoule or in vial. The finished product contains the following excipients: sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, polysorbate 20, sodium hydroxide and phosphoric acid, concentrated.
Except for the active substance, all the other components used in the composition of the medicinal product as well as the solvent comply with specific European Pharmacopoeia (Ph.Eur.) or United States Pharmacopoeia (USP) monographs. Moreover, these excipients are known to be widely used in the pharmaceutical industry.

Active substance
The active substance is a recombinant human luteinising hormone (r-hLH, lutropin alfa). Lutropin alfa has been extensively characterised using traditional physico-chemical, biological and immunological techniques (e.g. terminal amino acid sequencing, peptide mapping, electrophoresis, chromatographic analysis, bioassay, etc.) as well as state-of-the-art analytical procedures (e.g. mass spectrometry). Lutropin alfa is a heterodimeric glycoprotein, composed of two non-covalently linked and non-identical subunits, designated as α and β). The α-hLH subunit, common to all the gonadotrophin hormones (e.g. FSH), is 92 amino acid residues in length including two sites of N-linked glycosylation on Asn52 and Asn78. The β-hLH subunit, which is hormone specific, is 121 amino acid residues in length including one site of N-linked glycosylation on Asn30. The α-hLH and β-hLH subunits present five and six intrachain disulfide bridges, respectively. The molecular weights of the α-hLH and β-hLH subunits were determined by mass spectrometry as approximately 14kDa and 15kDa, respectively.
Since it is a glycoprotein, lutropin alfa is a mixture of isoforms and the microheterogeneity was well documented. The primary structure, for both the α– and β–subunits, has been demonstrated to correspond to that of the native peptides. Lutropin alfa presents N- and C-terminal heterogeneity. Based on the data provided by the company, it could be concluded that this N- and C-terminal heterogeneity has no impact on the biological activity of the active substance.
As for other glycosylated proteins, the structure of the carbohydrate chains attached to the peptide backbone is of major importance for the biological activity. Particular attention has thus been paid to the post-translational modifications detected in r-hLH. It has been demonstrated that the N-glycosylation sites, expected on each subunit are indeed present. In addition, glycan structures have been studied using mass spectrometry and glycan mapping. Although the complexity of the mass spectra demonstrated the high heterogeneity of the active substance due to the presence of these

oligosaccharide chains, the batch-to-batch consistency in terms of glycoform pattern of r-hLH is satisfactorily documented.
Overall the characterisation of the molecule has been well conducted and allows to conclude that r-hLH is structurally comparable to urinary- and pituitary-derived hormone, although not strictly identical, due to slight differences in post-translational modifications.

Developement genetics and cell bank system
The production process of lutropin alfa uses a transformed Chinese Hamster Ovary (CHO) host strain, which has been comprehensively described in the application. This strain was prepared by co-transfection into the genome of the parent CHO cell line of the two genes of interest coding for the α-hLH and β-hLH subunits. After transfection and selection, one subclone was chosen for further process development and was used to establish the Master Cell Bank (MCB). The methods used to establish the MCB have been well described and involved standard techniques widely used in DNA recombinant technology.
The preparation as well as maintenance (location and storage conditions) of the Master Cell Bank (MCB) and Working Cell Banks (WCB) are described in detail in the documentation. Approximately the same protocol was applied for both the MCB and the WCB expansion process. Characterisation studies (phenotypic as well as genotypic testing) of the various cell banks were carried out using classical tests. All vials tested from each cell bank were found to be free of microbial contamination (bacteria/fungi and mycoplasma). In addition, viral safety has been well documented and is not a matter of concern. Genetic stability has been demonstrated and the expression construct has also been validated at a generation number well beyond the intended production limit.

Fermentation and purification
The fermentation process, from the cell culture inoculum expansion to the final cell harvest, has been adequately described in the application. The equipment and dedicated facilities as well as cleaning in place and sterilisation procedures are satisfactorily documented. The composition of the various culture media (including the origin of the various components) as well as the way to prepare the culture media used in the fermentation process have been thoroughly documented. The various relevant parameters recorded during each phase of the bioreactor cell culture process (temperature, pH, dissolved oxygen, overpressure, etc.) have been documented in detail. In-process controls assure appropriate cell growth and the absence of microbial contamination.
The downstream purification process leading to the r-hLH bulk has been described in detail. Each harvest is clarified, concentrated, dialysed by ultrafiltration, sterile filtered and stored before further processing. The purification proceeds with subsequent chromatographic steps followed by ultrafiltration for the removal of viruses, concentration by ultrafiltration and final 0.22 µm filtration. A production batch of purified r-hLH bulk solution is defined as the material that has been processed as a single entity through the purification process. The various raw materials (including resins and filter membranes) as well as the composition of the various reagents, solutions and buffers used in the purification process for regeneration and sanitisation of purification columns and filters are listed in the documentation. The various in-process monitoring and control parameters are presented in detail for each purification step.
The production process of the active substance, which complies with Good Manufacturing Practice (GMP) requirements, has been adequately validated. These studies are documented in detail in the dossier. The various critical steps of the production process, from the cell culture to purification of r-hLH have been identified.
Based on the results obtained regarding the upstream (cell culture) as well as the downstream (purification) processes, the capacity, robustness and consistency of the production process are satisfactory and lead to an active substance bulk with a reproducible good quality.

Impurities
As regards removal of impurities during the purification process, detailed investigations have been performed. In general, satisfactory in-process control results were reported. Cell culture derived proteins are controlled in the bulk by using a validated ELISA. In addition, the absence of contaminating proteins is tested using an electrophoretic purity test. Potential microbiological and viral contamination is considered adequately controlled. Oxidised forms of the active substance are

controlled by chromatography. Aggregates and dissociated subunits of lutropin alfa are controlled by appropriate methods.

Routine tests and specifications of active substance

A total of five batches of r-hLH active substance, representative of the intended full-scale production process, are provided in the documentation along with information on batch size, date of production, and use. The five batches are derived from three cell culture runs.

The current analytical methods and specifications for the release of the active substance ensure consistent quality of the recombinant human luteinising hormone with respect to identity, purity, potency, and safety. The tests selected to be performed on a routine basis are satisfactory; their proposed limits are also considered as acceptable. However, considering the batch analysis results provided on five r-hLH active substance batches, the company committed to monitor future batches of active ingredient and to tighten some of the specifications if appropriate.

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

The *in vivo* biological activity was determined using an appropriate bioassay. Data on *in vivo* biological activities along with corresponding specific biological activities, provided for different batches, show a good consistency. In addition, immunological characterisation, based on immunospecific activity determination, further demonstrate inter-batch consistency. At the time of submission, no International Reference Standard had been established for r-hLH. After extensive characterisation studies, one specific batch has been selected as in-house reference standard. This approach is acceptable as an interim solution until an international r-hLH reference standard is established as part of a post-approval commitment.

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

Stability of active substance

The stability of the r-hLH active substance has been studied on four batches originating from the production site (Laboratoires Serono S.A., Aubonne, Switzerland) and seven smaller scale batches originating from the development site. The various batches have been stored at the recommended storage temperature. Stability testing is planned to continue until 36 months. In light of the good stability profile it was considered acceptable to use a 30-month storage period at the recommended storage temperature for the active substance. The company committed to provide additional stability data at month 30 as soon as available.

Other ingredients

All but one excipient used to formulate the medicinal product are described in a European Pharmacopoeia monograph and are quality controlled accordingly. The exception is the sodium dihydrogen phosphate monohydrate which meets the USP requirements. This was considered acceptable since only the dihydrate form is described in the European Pharmacopoeia.

Packaging material

Immediate packaging materials of the powder for injection (i.e. 3ml nominal capacity colourless Type I glass vial and grey W1816 bromobutyl lyophilisation stoppers) are described in the documentation.

The solvent for reconstitution (sterile water for injections) is contained either in a 2ml, one point cut ampoule made of colourless ammonium sulphate-treated glass (Type I) conforming to Ph.Eur. ii) or in a 2ml vial of colourless glass (Type I) conforming to Ph.Eur. and closed using a teflon-coated rubber stopper.

Studies to evaluate the compatibility between the reconstituted lutropin alfa solution and the container/closure system were performed. These studies showed that r-hLH is prone to adsorb to surfaces and that adsorption is varying from batch to batch. For the production of Luveris, an overage

is used to compensate for loss and to ensure that sufficient active substance is delivered to the patient. However, given that the submitted data did not allow to evaluate properly the size and variability of these adsorption phenomena and to evaluate the impact on the dose delivered to the patient, the company committed to further investigate adsorption losses as part of their post-authorisation commitments. Considering the possible concomitant administration of r-hFSH in clinical practice, adsorption phenomenon was also studied using a mixture of r-hLH and r-hFSH.

Product development and finished product

Various formulations have been tested to select the appropriate buffering, bulking, stabilising, anti-aggregation agents, and their corresponding concentrations. The choice of the various excipients as well as the dosage strength have been well justified for the powder. The composition and the pharmaceutical presentation are very classical for a recombinant protein intended to be administered by subcutaneous injection. Process development studies were conducted on some steps of the manufacturing process to evaluate the impact of these steps on the integrity of the active substance. Optimal process parameter ranges were established.

Method of preparation
Luveris is manufactured as vials of powder for injection. The manufacturing process, which complies with Good Manufacturing Practice (GMP), has been described in sufficiently detail. It takes place in a dedicated facility at Laboratoires Serono S.A., Aubonne, Switzerland. Briefly the calculated amount of active substance in solution is mixed with the excipient solution to obtain the formulated bulk solution which is subsequently sterile filtered and filled in vials under aseptic conditions before freeze-drying, stoppering and capping. The manufacturing process has been adequately validated and is monitored using satisfactory in-process controls.
The manufacturing process of the water for injections, provided in vials or ampoules, is classical and has been described in detail. The manufacturing process, which complies with GMP, takes place in dedicated facilities at Pharma Hameln, Germany (for the ampoules) and Gensia Sicor Pharmaceuticals Inc, USA (for the vials).
For the validation of the manufacturing process, results on three batches of the finished product manufactured at the intended commercial scale have been provided. The data showed that the finished product consistently met the proposed specifications and demonstrated that the manufacturing process is consistently reproducible.

Specifications of the finished product
The proposed tests and limits allow to check each batch of the finished product for identity, purity, safety, and potency. All test methods intended to be used for routine testing, except those from the European Pharmacopoeia, have been validated for accuracy and reliability. In general, the proposed specifications are acceptable, and the limits are reasonable and based on the experience already gained.

Stability of the finished product
Stability of the finished product has been studied for three batches manufactured at the intended industrial commercial scale. The stability protocol was designed to provide information on the stability of the finished product at the recommended storage temperature (i.e. +25°C) as well as under accelerated conditions. Based on these studies the shelf life of Luveris is 12 months at ≤25°C. After reconstitution, the product should be used as soon as practical.

Viral safety
No adventitious viruses or retroviruses were detected in all the tests performed and therefore, the tested cell lines (MCB or WCB or EPDB-1) exhibit a satisfactory level of viral safety. It can be concluded that cell banks were validated in accordance with the CPMP/ICH note for guidance on quality of biotechnological products and can be used as safely as possible as cell substrate for r-hLH production.
The manufacturing process for lutropin alfa requires cell culture media containing Foetal Bovine Serum (FBS), which is of bovine origin. FBS was derived from animals sourced in USA or Canada, which are BSE-free countries, and has been prepared in accordance with the "Note for Guidance on

minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (CPMP/BWP/1230/98). Besides FBS, the manufacturing process of lutropin alfa involves the use of two other reagents of biological origin. Both are of porcine origin and their manufacturing process ensures that no viruses are introduced into the manufacturing process by these reagents.
Overall, the viral safety of lutropin alfa is assured by, i) the satisfactory viral testing of cell banks, biological reagents, and unprocessed bulk, ii) the robustness of the production process and iii) the satisfactory cumulative reduction factors achieved by the purification process. Despite the absence of a specific viral inactivation step, it can be stated that the production process is effective to clear potential viruses that could be present in the un-purified product.

Discussion on the chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with the requirements in the Note for Guidance on Production and Quality Control of Medicinal Products Derived by Recombinant DNA Technology as well as other relevant guidelines. The information provided in the application demonstrated consistent production of lutropin alfa achieving a well-defined quality for the active substance and the finished product as well as for the solvent for reconstitution. The fermentation and purification processes of the active substance are adequately controlled. Lutropin alfa has been well characterised using state-of the-art methods with regard to its physicochemical characteristics. As a glycoprotein, the active substance is a mixture of isoforms and the microheterogeneity has been well documented. The manufacturing process of the finished product, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail and product specifications are adequate. In general, methods to control the quality of the product are adequate. Moreover, this is a product of biological origin for which all the virological aspects have been satisfactorily addressed. Stability data support a shelf-life of 12 months for the finished product.
Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Luveris is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

In vitro, standard competition binding analysis indicated that r-hLH and pituitary human LH bind with similar affinity to the specific LH/hCG receptor.
Bioactivity tests measuring seminal vesicle weight gain in immature male rats (Van Hell Bioassay) demonstrated that r-hLH was able to stimulate the steroidal secretion of cells bearing LH receptor.
In vivo, the general pharmacodynamics of Luveris were studied in mice, rats and guinea-pigs. Studies were designed to identify the effects of 200, 2000 and 20000 IU/kg r-hLH doses. These studies evaluated lutropin alfa's effect on general behaviour and activity, on the central and autonomic nervous system, on the gastrointestinal system and on renal function. The effects of lutropin alfa on uterine motility were also determined in female rats. These studies revealed no adverse effects up to a dose of 20000 IU/kg.
In vivo, the activity of r-hLH on follicular development was tested in adult female monkeys pre-treated with a GnRH antagonist prior to stimulation with r-hFSH alone, or with r-hFSH associated to r-hLH in a 1:1 ratio. No significant effect of r-hLH on follicular growth was observed but the regimen with r-FSH and r-hLH resulted in increased oestradiol concentrations compared to the regimen with FSH alone.
The effects of r-hLH on oocyte maturation, luteinisation and progesterone production was tested in the same non-human primate model and was compared to pituitary human LH (p-hLH) and to human chorionic gonadotrophin (hCG) respectively. Results reflected the anticipated effects on oocyte meiosis, ovarian luteinisation and progesterone production and were as follows:
1) serum progesterone was slightly higher after hCG than p-hLH or r-hLH;

2) circulating LH activity was raised for 36 to 48 hours after r-hLH and p-hLH but for more than 48 hours after hCG;
3) effects of a single administration of r-hLH on oocyte maturation and follicular luteinization were less significant than with two doses which were more comparable to those of p-hLH but less intense than with hCG;
4) regarding *in vitro* progesterone production of the granulosa cells, r-hLH was identical to pituitary human LH. hCG had a more powerful effect on progesterone production due probably to its longer half life.

General pharmacodynamic tests did not show any evidence that r-hLH has pharmacological actions that may affect its safety on therapeutic use. Drug interactions studies and enzyme induction/inhibition studies were not provided. This was considered acceptable given the likelihood that r-hLH behaves like hLH.

Pharmacokinetics

Pharmacokinetic absorption, distribution, metabolism and excretion studies were performed in rats after either intravenous (IV) or subcutaneous (SC) administration of a single dose of radiolabelled ^{125}I-lutropin alfa. Following IV administration in rats, the terminal half-life was 3 hours. After SC administration, the absolute bioavailability was 61% and the terminal half-life was 7 hours. There was no difference between pregnant and non-pregnant animals although C_{max} (maximum concentration in plasma) tended to be higher in pregnant animals. Radioactivity was almost completely recovered in the excreta within one week, mostly in the urine (about 90% after SC injection), the rest in the faeces (less than 10 % after SC injection). Biliary excretion was very low. Results were similar after SC and IV injection. In lactating rats, radioactivity in milk was greater than or equal to that in plasma. Apart from the strong uptake of the radioactivity from the thyroid, some uptake has been observed in kidneys, stomach and in the target organs such as ovaries. There was only a low transfer to foetuses and to the placenta. The metabolic pathway of r-hLH was not clearly investigated. As the pharmacokinetic profile of r-hLH was similar to that of p-hLH and urinary h-LH (u-hLH), it can be assumed that they follow the same metabolic pathway.

Single dose studies

Pharmacokinetics of r-hLH after administration of a single dose was also investigated in the monkey and was compared to that of pituitary LH and urinary LH. The serum concentrations of r-hLH were determined using an immuno-assay (MAIAclone). Linearity was demonstrated between doses ranging from 63 to 400 IU/kg but not for doses between 10 to 63 IU/l (this may be due to the limited sensitivity of the method used for determining serum levels of LH).

Because of the occurrence of antibodies in three animals, results from an intramuscular/subcutaneous cross-over study have to be considered with caution. Half-lives after intravenous, intramuscular (IM) and subcutaneous administration were similar. The bioavailability was slightly higher for the IM route than for the SC route (0.6 *versus* 0.5). The half-life of r-hLH was comparable to that of pituitary and urinary hLH.

Repeated dose studies

Pharmacokinetic studies after administration of repeated doses were performed both in the rat and in the monkey. In the rat, the pharmacokinetic profile following SC administration was assessed using radioactivity and immunoassay measurements of LH. The most valid information was provided by the immunoassay data. AUC and elimination half-life were similar to those obtained after single dose administration showing that no accumulation occurred after repeated doses. In the monkey, pharmacokinetic parameters were determined and compared following IV, IM and SC administrations. The elimination half-life was higher after SC injection and similar for IV and IM administration. Overall, pharmacokinetic assessment during repeated dose studies was hampered by the development of antibodies.

Conclusion

In summary, pharmacokinetic and metabolism studies have been performed taking the human protein nature of r-hLH into account implying antibody formation in animals after multiple

doses. In monkeys, absorption from the SC injection was rapid and consistently amounted to about 50% after single and repeated daily injections. The elimination half-life was 11-14 hours. Accumulation is minimal. The clearance was around 0.03 $l \cdot h^{-1} \cdot kg^{-1}$ and the volume of distribution at steady-state was around 0.1-0.3 l/kg. Repeated administration of r-hLH to rats and monkeys caused well known pharmacological and morphological effects which were more exaggerated in the rat which differs greatly from humans with respect to the oestrous cycle and hormonal metabolism. Throughout the repeated dose investigations, predictable effects on mammary glands, adrenals and thymus were observed.

Toxicology

All the toxicity studies were performed in compliance with Good Laboratory Practice. r-hLH was administered intravenously and subcutaneously as the product is intended for subcutaneous administration. A dose range up to a high multiple of the anticipated human dose range was used to assess the acute toxicity of r-hLH in male and female rats and monkeys. The clinical intended therapeutic schedule is a single daily injection for up to 5 weeks followed by further cycles of treatment in case of failure of the first cycle. Short-term (two and four weeks) and long-term (3 month) repeated dose studies were performed. Three doses or more, ranging from 10 times to 4000 times the therapeutic dose of 1.25 IU/kg/day were tested. A specific immunoassay was used to measure the circulating levels of LH.

Single dose toxicity
Much higher doses of r-hLH than the anticipated clinical dose did not cause systemic toxicity in rats and monkeys when given as a single IV or SC injection. It is important to note that although SC injection is the intended clinical route, IV administration, which allowed complete bioavailability, did not result in toxicity. In addition, local tolerance was good. Observed changes in the rat testes were expected based on the pharmacological actions of LH.

Repeated dose toxicity
Repeated IV and SC administration of r-hLH for up to four weeks appeared to be well tolerated in both male and female rats and monkeys at dose levels up to 5000 IU/kg dose. Increasing the duration of repeated SC administration in female animals of both species with dose of up to 1000 IU/kg was also well tolerated. Most of the pharmacological and morphological modifications (e.g. increase in the size and weight of seminal vesicles, atrophy of the thymus, and in rats only, increase in the size and weight of prostate, vacuolation of the adrenal cortex, increase in pituitary weight) observed could be explained by the pharmacological action of r-hLH. Given that the rat differs greatly from humans with respect to the oestrous cycle and hormonal metabolism, is it known that the observed effects are more exaggerated in rats than in humans.
Repeated administration of high doses of LH to rats disrupts the cyclic control mechanisms resulting in morphological changes of the reproductive system including the development of follicle cysts, an increase in the size and number of corpora lutea, uterine mucosa hyperplasia, mucification of the vaginal mucosa and mammary gland hyperplasia. It should be noted that the repeated administration of lutropin alfa resulted in antibody formation in all species studied. The presence of antibodies was more apparent for the SC route than for the IV route. Considering the presence of antibodies in the monkey and the weak hormonal response observed in the studies, results must be interpreted with caution. In particular no specific information regarding the neutralising potential of these antibodies was provided. Therefore, the chronic toxicity may have been underestimated.

Reproduction studies
Adequate reproduction toxicity was investigated in rats and rabbits. No materno-toxicity was observed at the high doses. In the rat, a lower fertility index, an increase in pre- and post-implantation losses, reduced foetal weight, and fewer live born pups were noted. The surviving F1 (i.e. first generation) pups had reduced body, testes and ovaries weight. The dose of 5 IU/kg/day can be considered as safe. r-hLH can be considered as not teratogenic in the rat and in the rabbit. Therefore, lutropin alfa is not expected to teratogenic in humans.

Genotoxicity
r-hLH did not appear to be genotoxic. *In vitro* studies in two bacterial species, which detect different types of point mutations, as well as in mammalian cells demonstrated that at concentrations up to 15,710 IU/ml or per plate, r-hLH did not cause point mutations. A further *in vitro* experiment in human lymphocytes showed that r-hLH did not induce chromosome aberrations or polyploid cells. *In vivo* studies in the mouse showed that at dose levels up to 200,000 IU/kg, r-hLH does not cause chromosomal fragmentation. Since the highest concentrations or doses of r-hLH used in these studies greatly exceeds the intended human dose by over thousands fold, these studies demonstrate that r-hLH is not a potential mutagen.

Carcinogenic potential
Carcinogenicity studies have not been performed with r-hLH as negative results were obtained in extensive mutagenicity studies. As r-hLH is claimed to be identical to native human LH and intended for short term therapeutic administration in human, the absence of carcinogenicity studies is justified. In addition, the CPMP Note for Guidance on Conditions Which Require Carcinogenicity (CPMP/140/95) states that carcinogenicity studies are not generally required for certain types of products including proteins produced by recombinant DNA technology.

Local tolerance
r-hLH was well tolerated at the injection site after single administration by IM route. Although the local tolerance should have been evaluated after a SC injection since lutropin alfa is intended for subcutaneous use, studies where the product had been administered subcutaneously did not question the good tolerance of the product.

Immunogenic potential
The immunogenic potential was tested in Guinea pigs and showed a moderate sensitisation after intradermal injection. The anaphylactic response was also tested in Guinea pigs. Some high dose animals died with acute systemic anaphylaxis after IV injection. However, this test is generally positive for products consisting of recombinant human proteins and is not predictive for the occurrence of such reactions in humans. In rats and mice, passive cutaneous anaphylaxis revealed a limited ability to induce allergic reactions. The passive hemagglutination test has showed a weaker antigenicity in mice than in guinea-pig.

Environmental risk assessment
Since native hLH enters the environment daily via excretion by healthy women, and since r-hLH is intended for the treatment of a relatively small number of women with FSH and LH-deficiency, the introduction of a small amount of r-hLH into the environment does not pose an environmental risk.

Discussion on toxico-pharmacological aspects
Overall, pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of lutropin alfa to induce ovulation. Results from the toxicology programme did not raise particular concerns for the safe use of lutropin alfa.

4. Part IV: Clinical aspects

Clinical pharmacology

Lutropin alfa is a recombinant human luteinising hormone, a glycoprotein composed of non-covalently bound α- and β-subunits. Luteinising hormone binds on the ovarian theca (and granulosa) cells and testicular Leydig cells, to a receptor shared with human chorionic gonadotrophin hormone (hCG). This LH/CG transmembrane receptor is a member of the super-family of G protein-coupled receptors. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce oestradiol,

supporting FSH-induced follicular development. At mid-cycle, high levels of LH trigger corpus luteum formation and ovulation. After ovulation, LH stimulates progesterone production in the corpus luteum by increasing the conversion of cholesterol to pregnenolone.
In the stimulation of follicular development in anovulatory women deficient in LH and FSH, the primary effect resulting from administration of lutropin alfa is an increase in oestradiol secretion by the follicles, the growth of which is stimulated by FSH.

Overview of Pharmacological Studies

Study	Type of Study	Product(s) tested	Doses & Route of administration	Total number of subjects
GF 6135	Open label, non-randomised, dose-escalating, comparative study	Luveris (reference product: Pergonal (hMG))	Luveris: 75, 300, 10 000 an 40 000 IU IV Pergonal: 300 IU IV (Single dose once per week Up to 10 weeks)	12
GF 6136	Open, random-order, cross-over study	Luveris	10 000 IU IV, IM, SC route (Single dose Up to 8 weeks)	12
GF 6137	Open, random-order, cross-over study	Luveris in association with Gonal-F 150 IU (follitropin alfa)	150 IU SC route (Single and repeated doses Up to 9 weeks)	12

Pharmacodynamics

A quantitative evaluation of pharmacodynamic effects of lutropin alfa in humans was not specifically performed. Some data were obtained from study GF 6137 after 7 days of combined r-hLH and r-hFSH treatment (150 IU of each hormone daily). The effects on oestradiol, progesterone, and inhibin levels and follicular development were investigated. The expected effects of FSH were not affected by co-administration of LH. Treatment with a GnRH analogue was used to achieve suppression of endogenous LH, which was necessary to assess the pharmacodynamic effects of lutropin alfa in women. However, a complete suppression was difficult to achieve and residual LH remained at detectable levels. The limited pharmacodynamic data are acceptable since:

- modifications between the naturally occurring human pituitary LH and lutropin alfa are relatively minor,
- the pre-clinical assessment of lutropin alfa has confirmed the receptor binding affinity and the intrinsic bioactivity of r-hLH,
- patients with hypogonadotrophic hypogonadism (HH) who were included in the clinical study can be considered as the best human model to assess the activity of the LH preparation (Luveris is intended for treatment of this restricted patients population only).

Luveris was well tolerated in all Phase I studies: no serious adverse events or significant changes in vital signs or in laboratory tests results were noted in any subject throughout these studies. Non serious events were time-dependent hot flushes attributable to the low oestradiol serum levels induced by the GnRH-agonist treatment. These were all of mild to moderate severity.

Pharmacokinetics

Pharmacokinetics were not evaluated in women with hypogonadotrophic hypogonadism but three studies have been conducted in healthy women (18-35 years) in whom endogenous LH secretion had been down-regulated by administering a GnRH analogue. These studies examined pharmacokinetics and safety of r-hLH. r-hLH and endogenous LH concentrations in serum and urine were measured using an immunoradiometric assay specific with respect to the other glycoprotein hormones (cross-reactivity with human FSH, TSH, and GH was less than 0.25%; cross-reactivity with hCG was about 3%). The pharmacokinetics were confirmed using a less precise (and possibly less specific) *in vitro* bioassay measuring the production of progesterone by a cell line responsive to LH stimulation (MA-10 Leydig tumor cells).
The lack of pharmacokinetic studies in the relevant target population (i.e. women with hypogonadotrophic hypogonadism) was a particular concern since a dose-linear relationship was not demonstrated with doses below 300 IU in healthy gonadotrophin-suppressed women probably because of residual endogenous LH-secretion. With the currently available procedures for analysing serum concentrations of LH (and r-hLH), injection of the lowest doses that will elicit a physiological "LH" effect (about 75 IU) will result in serum concentrations of LH very close to the detection limit of the assay. Therefore, it is difficult to obtain precise pharmacokinetic information in the physiological dose-range. Taking into account the sensitivity of the available immunoassay the lack of pharmacokinetic studies in women with hypogonadotrophic hypogonadism was considered acceptable.

IV administration
Following intravenous administration of Luveris, lutropin alfa was rapidly distributed with an initial half-life of approximately one hour and eliminated from the body with a terminal half-life of about 10 hours. The steady-state volume of distribution was around 8 liters. Lutropin alfa showed linear pharmacokinetics overdoses ranging from 300 to 40 000 IU. Total clearance is around 2 l/h, and less than 5% of the dose was excreted in the urine. The mean residence time was approximately 5 hours.
The analysis for a dose of 75 IU was difficult and probably unreliable due to presence of endogenous LH because the down-regulation did not completely inhibit LH secretion from the pituitary. The absence of information in this dose range (< 300 IU) cannot substantiate the intended therapeutic regimen and the dose adjustment recommendations. In spite of a statistical difference between the values obtained for the Area Under the Curve (AUC), the serum pharmacokinetic profile of r-hLH was comparable to that of urinary hLH (u-hLH) except that the renal clearance of u-hLH was greater than that of r-hLH.

IM and SC administration
Following IM and SC administration, the pharmacokinetic profile was determined only after a single dose. Immunoassay data did not show any statistical difference in the pharmacokinetic profile for the IM and SC routes of administration. Considering the longer terminal half-life after IM and SC administration (about 18 hours), elimination of r-hLH by the extra-vascular route is rate-limited by the absorption at the site of injection. The absolute bioavailability of r-hLH after IM or SC administration was approximately 55*%.*

Interaction studies
As r-hLH is intended to be co-administered with FSH, interaction of Luveris with an r-hFSH preparation was investigated. There was no pharmacokinetic interaction with follitropin alfa when administered simultaneously. The bioavailability of r-hLH (150 IU) remained unchanged when co-administered with r-hFSH (150 IU). After multiple dosing there was a slight accumulation of LH (about 1.5-fold) whereas FSH accumulated by about threefold. However, because of the incomplete suppression of endogenous LH, these results may not be reliable.

Clinical efficacy

Tabular overview of Clinical studies

Study	Study Design	Product(s) tested	Dosage	Duration of treatment	Total Number of subjects
GF 6253	Open, randomised, dose-finding, pivotal, multicenter	Luveris	0, 25, 75, or 225 IU/day SC daily in association with follitropin alfa (Gonal-F 150 IU)	1) for up to 21 days/cycle 2) for up to 3 cycles	N=38
GF 6905	Open, randomised, dose-finding, multicenter	Luveris	0, 25, 75 or 225 IU/day SC daily in association with follitropin alfa (Gonal-F 150 IU)	1) for up to 21 days/cycle 2) for up to 3 cycles	N=40

Dose-response studies and main clinical studies

Two open randomised dose-finding studies were conducted, one in Europe (GF 6253) and one in the USA (GF 6905). These trials did not include an active comparator (hMG or pulsative GnRH) because of the very small target population. The design of the two studies was similar as regards dosing and efficacy endpoints. However, the criteria for HH were stricter and more relevant in the European study, which only included women with a baseline serum LH below 1.2 IU/l. The US study accepted a level $\leq$10.8 IU/l, although it is acknowledged that women with less severe LH-deficiency respond to FSH treatment alone. The primary endpoints were objective, i.e. measurement of follicle size by ultrasound examination and measurement of oestradiol and progesterone concentrations in plasma. The primary efficacy endpoint was development of a "functional" follicle. Three criteria had to be fulfilled:

1. at least one follicle with a mean diameter ≥17 mm. 2. preovulatory E_2 serum level above 400 pmol/l. 3. mid-luteal phase P_4 level above or equal to 25 nmol/l. Against this background the non-blinded design seems acceptable. Secondary efficacy endpoints included oestradiol level per follicle at mid-cycle, number of follicles at mid-cycle, endometrial thickness at mid-cycle and pregnancy (for those wishing to conceive).

The European study was considered to be the pivotal study. This study included 38 patients, of which 34 could be evaluated and included in the efficacy analysis. The US study included 43 patients of which 40 could be evaluated.

The patients were randomised into four groups receiving either 0, 25, 75 or 225 IU of r-hLH together with a fixed dose of 150 IU of r-hFSH daily. The specific dose of LH was given in the first cycle called A. This cycle was used for the efficacy analysis. Some patients were treated in additional cycles called B and C. In these cycles the dose of LH was increased if there was no response to the LH dose given in the prior treatment cycle and decreased if there had been a response in the prior cycle.

The table below summarises the results of the dose finding studies. The number of patients fulfilling the primary efficacy endpoint based on all three criteria and including patients who did not receive hCG due to excessive follicular development (risk of OHSS, ovarian hyperstimulation syndrome) as a treatment success are given. For study GF 6905, which used less stringent criteria for HH, the results of the subgroup with pre-treatment LH below 1.2 IU/l are presented separately.

Results of clinical trials expressed as the percentage of patients fulfilling the primary efficacy endpoint

Study	**GF6253 European pivotal**	**GF6905 US**	**GF6905 LH <1.2 IU/l Subset**
Patients	n=34	n=40	n=15
r-hLH Treatment:			
225 IU/day	8/10 (80%)	6/9 (67%)	3/4 (75%)
75 IU/day	6/9 (67%)	8/11 (73%)	2/3 (67%)
25 IU/day	1/7 (14%)	9/9 (100%)	5/5 (100%)
0 IU/day	0/8 (0 %)	7/11 (64%)	0/3 (0%)
P value*	0.0001	0.774	0.039

* Cochran-Armitage Trend test

Based on these results a starting dose of 75 IU/day of r-hLH has been recommended. The company had originally claimed that in some patients optimal follicular development may require up to 10 micrograms (225 IU/day) lutropin alfa. However, from the clinical trials, there was no evidence that 225 IU/day is more effective. An increase of dose in case of treatment failure did not appear to increase the success rate. As a result, 75 IU/day lutropin alfa is the only recommended dose.

Results obtained for the control group (patients treated with 0 IU/day lutropin alfa) revealed that in patients fulfilling very strict criteria of HH, it is necessary to administer r-hLH together with r-hFSH in order to obtain follicle maturation. Efficacy of LH substitution by lutropin alfa in hypogonadotrophic patients with baseline LH levels higher than 1.2 IU/l has not been shown.
When women with HH undergo treatment with LH and FSH it is generally with the purpose of becoming pregnant. However, it is accepted that the combined surrogate endpoint is relevant and adequate proof of efficacy in women with HH. However, the clinical pregnancy rate obtained with r-hLH at 75 IU daily dose, can be considered similar to those published in the literature in this indication either with hMG or with a pulsatile GnRH administration.

Clinical safety

Patient exposure
All patients (n=78) were included in the safety analysis, reporting the incidence and severity of adverse events (AEs) including local tolerance at the injection site, and representing a total of 83 cycles. In addition, occurrence of potential antibodies to both r-hLH and r-hFSH was assessed.

Adverse events and serious adverse events/deaths
Among the 133 adverse events that occurred in 42 patients, the most commonly reported adverse events were pelvic or abdominal pain, headache, breast pain, nausea, ovarian cysts, and dysmenorrhoea. Somnolence has also been reported. Such symptoms and signs are commonly reported in women who receive gonadotrophins to stimulate ovulation. In study GF6253, three patients had abdominal symptoms suggestive of OHSS (ovarian hyperstimulation syndrome). However, the company has confirmed that there were no cases of actual OHSS in this clinical trial. In both protocols hCG administration was withhold when assessment of estrogen levels and a multifollicular response indicated a significant risk of OHSS. This occurred in 5 out of 38 patients in study GF 6253 and in 5 out of 40 patients in study GF 6905.
Local tolerance was acceptable based on 985 injections. Moderate reaction at the injection site was recorded in 0.9% of injections. Severe swelling and bruising were reported in one patient in the 75 IU r-hLH group in study GF 6905.
The possible immunogenicity of the recombinant gonadotrophins was investigated by detection of antibodies in samples collected before, during and after treatment. In GF 6253 study: negative results for antibodies directed against LH and FSH were obtained for all 34 patients treated with one cycle as well as for 9 patients who have started a second cycle of treatment and for 5 patients who have received a third cycle. In study GF6905, 37 out of 40 serum samples were negative for antibodies to both FSH and LH.

Laboratory findings
Standard serum biochemistry tests during and after therapy did not show any clinically significant changes from baseline.

Safety in born children
Data on children born as a result of the treatment given in protocols GF 6253 (study period 1993-1995) and GF 6905 (study period 1994-1997) have not been presented but the company confirmed that adverse events in these children had not been reported. The company committed to follow and report on the development of the children born following stimulation with Luveris.

Discussion on clinical aspects

Dose regimen
The company had originally claimed that in some patients, optimal follicular development may require up to 225 IU/day lutropin alfa. However, this claim was not supported by clinical data and 75 IU/day lutropin alfa is the only recommended dose. Efficacy of Luveris was assessed in combination with a fixed dose of 150 IU of a FSH preparation. Depending on the response the FSH dose may need adaptation. The dose of FSH may be increased by preferably 37.5-75 IU at 7-14-day interval and treatment may be extended for up to 5 weeks.

Clinical efficacy
Hypogonadotrophic hypogonadism is a very rare condition, which explains the limited number of patients included in the clinical trials and the lack of comparative clinical trials. The lack of active comparator-controlled studies has been considered as acceptable as such studies would require an unrealistically high number of patients, based on the incidence estimated for this pathology. Moreover, it would involve a comparison of the effect(s) of the FSH components of r-hFSH and hMG in addition to an evaluation of the effect(s) of r-hLH. Even though a head to head comparison of r-hFSH/r-hLH versus hMG would be optimal, it is considered virtually impossible to conduct. Based on incidence estimates it is expected that about 1000 patients per year in the EU would need treatment for this type of female infertility.
The most important issue was the question of target population for treatment with r-hLH . The clinical data provided did not support the originally claimed indication for Luveris in the treatment of all patients with LH and FSH deficiency. Therefore, the use of Luveris is restricted to patients with severe LH and FSH deficiency, i.e. with baseline serum LH level below 1.2 IU/l. However, when assessing the endogenous serum level of LH, inter-laboratory variation in LH measurements should be taken into account.

Conclusion on safety
The safety data demonstrates that r-hLH is very safe. The adverse events reported revealed no unexpected or serious adverse events attributable to r-hLH. The period of r-hLH treatment in the clinical trials reflects the period of treatment for the proposed indication. The number of patients who have received r-hLH is relatively small, and thus the safety database is not as large as is often the case for new medicinal products. However, on the basis of knowledge accumulated for urine derived LH and since the structure of r-hLH is very similar to the LH produced naturally in humans, lutropin alfa is not likely to cause unexpected adverse events.

5. Overall conclusions and benefit/risk assessment

Quality
Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Luveris is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral

safety and batch to batch consistency has been documented and the relevant tests will be performed according to the agreed specifications (specifications are attached).

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

Clinical efficacy
The results from clinical studies support the use of lutropin alfa in association with a follicle stimulating hormone (FSH) preparation to stimulate follicular development in women with severe LH and FSH deficiency as defined by an endogenous LH level < 1.2 IU/l, i.e. to induce ovulation in anovulatory women with hypogonadotrophic hypogonadism.

Clinical safety
The safety data demonstrates that lutropin alfa is safe. The adverse events reported revealed no unexpected or serious adverse events attributable to lutropin alfa. The period of lutropin alfa treatment in the clinical trials reflects the period of treatment for the proposed indication. The number of patients who have received lutropin alfa is relatively small, and thus the safety database is not as large as is often the case for new medicinal products. However, on the basis of knowledge accumulated for urine derived LH and since the structure of lutropin alfa is very similar to the LH produced naturally in humans, lutropin alfa is not likely to cause unexpected adverse events.

Benefit/risk assessment

Benefit
Clinical studies have demonstrated the efficacy of lutropin alfa in association with a follicle stimulating hormone (FSH) preparation in stimulating follicular development in women with severe LH and FSH deficiency (women with hypogonadotrophic hypogonadism). Current treatment of severe HH consists of urine derived human menopausal gonadotrophins (h-MG) since the patients need both FSH and LH. Follicular development can be achieved with FSH alone, but inadequate follicular oestradiol production may lead to impaired endometrial growth and failure to form a functional corpus luteum when exposed to hCG. Current preparations of hMG contain FSH and LH in combination. With Luveris, luteinising hormone becomes available separately from FSH which allows to individualise dosing of the two gonadotrophins.

Another approved treatment for severe HH consists of gonadotrophin releasing hormone (GnRH) that stimulates endogenous FSH and LH secretion when administered every 60 to 120 minutes over a week via a portable pump. However, such treatment requires a normal pituitary function. Lutropin alfa together with FSH can be used in women with a deficient pituitary function.

Risk
Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Luveris is considered to be acceptable when used in accordance with the conditions defined in the SPC. Viral safety has been documented.
The safety data demonstrates that lutropin alfa is safe. The adverse events reported revealed no unexpected or serious adverse events attributable to lutropin alfa. Although the safety database is at current not large, on the basis of knowledge accumulated for urine derived LH, lutropin alfa is not likely to cause unexpected adverse events.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Luveris was favourable when lutropin alfa is used in association with a follicle stimulating hormone (FSH) preparation to stimulate follicular development in women with severe LH and FSH deficiency as defined by an endogenous LH level < 1.2 IU/l.

The Committee for Proprietary Medicinal Products recommends the granting of a marketing authorisation for Luveris, subject to the chemical, pharmaceutical and biological, as well as clinical follow-up measures undertaken by the company.

The approved Summary of Product Characteristics, Patient Leaflet and Labelling are annexed to the CPMP Opinion.