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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-322**

**Pharmacology Review(s)**

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-322

Review number: 1

Serial number/date/type of submission: 000/4-30-2001/original application

Information to sponsor: Yes ( ) No ( \* )

Sponsor and/or agent: Serono, Inc. Norwell, MA

Manufacturer for drug substance: Laboratoires Serono S.A. Aubonne, Switzerland

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.

Division name: Reproductive and Urologic Drug Products

HFD #: 580

Review completion date:

Drug:

Trade name: Luveris

Generic name (list alphabetically): Lutropin alfa

Code name: ATC G03 GA Gonadotropins

Chemical name: Recombinant human luteinizing hormone (r-hLH)

CAS registry number: 152923-57-4

Mole file number: -

Molecular formula/molecular weight:

Structure:

Luteinizing hormone (LH) is a heterodimeric glycoprotein from the same family as the pituitary gonadotropins (human follicle stimulating hormone and human chorionic gonadotropin) and human thyroid stimulating hormone. It consists of two non-covalently linked sub-units (designated as alfa and beta) of 92 and 121 amino acids, respectively.

Relevant INDs/NDAs/DMFs: IND 48,934; NDA 21-149 (Ovidrel, Choriogonadotropin alfa)

Drug class: Human luteinizing hormone of recombinant origin. Therapeutic class by indication is infertility

Indication: 1C

Clinical formulation: Formulation used in clinical trials is as given in the following table:

Name of ingredient	Unit formula	Function
<b>Drug substance</b>		
Recombinant human luteinizing hormone	3.4 ug (equiv. to 75 IU)	
<b>Other ingredients</b>		
Polysorbate 20 USP	0.05 mg	⌈
Disodium phosphate dihydrate USP	0.825 mg	
Sodium dihydrogen phosphate monohydrate USP	0.052 mg	
Sucrose USP	47.75 mg	
Phosphoric acid, concentrated USP	q.s.	
Sodium hydroxide USP	q.s.	
⌈		⌋
<b>Solvent</b>		
Water for injection USP	1 ml	⌋
⌈		⌋
methionine ⌈	. The to-be-marketed formulation contains 0.1 mg L-	
		⌋

Route of administration: Subcutaneous

Proposed use: ⌈

⌋

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

## OVERALL SUMMARY AND EVALUATION:

**Introduction:** Luveris (lutropin alfa for injection) is a sterile lyophilized powder composed of recombinant luteinizing hormone, r-hLH using genetically modified Chinese Hamster Ovary cells. It is intended for co-administration with r-hFSH as a subcutaneous injection after reconstitution with sterile water for injection.

The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. Luveris is administered concomitantly with r-hFSH to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

Luteinizing hormone is a well understood protein hormone whose pharmacodynamic action is mediated through its binding to its surface-bound receptors on target cells leading to increased adenylyl cyclase activity.

**Safety evaluation:** The safety of r-hLH (Luveris) is based both on similarity of physical and chemical characteristics with its naturally occurring counterpart i.e., natural hLH and on the examination of 5 well controlled studies for the induction of ovulation in women with hypogonadotropic hypogonadism and pre-clinical toxicity studies.

Recombinant human luteinizing hormone, like its naturally occurring counterpart, is a heterodimer glycoprotein, composed of two non-covalently linked non-identical subunits, designated alfa and beta. The alfa subunit, which is common to all the gonadotropin hormones, is 92 amino acids in length and possesses two sites of N-linked glycosylation (Asn 52 and Asn 78). The B subunit, which is hormone specific, is 121 amino acids in length and possesses a single site of N-linked glycosylation (Asn 30). The primary structure of both subunits corresponds to that of the native peptides and the N-terminal heterogeneity of both subunits is identical feature observed in urinary and pituitary hLH. The C-terminus truncated form of B-subunit have been observed in u-hLH (urinary hLH) and p-hLH (pituitary hLH) and no full length species with an intact C-terminus has been detected in either u-hLH or p-hLH.

The main differences between recombinant and natural products, both of urinary and pituitary origin are that natural hLH glycans contain N-acetylglucosamine residues and their sulfated derivative while r-hLH glycans contain only sialylated species explained by the incapability of CHO cells to produce sulfated residues. These differences have little relevance to biological activity of the molecule. Deglycosated variants of LH and other gonadotropins bind well to their receptors, however, unlike the glycosylated forms, they are unable to activate significant adenylyl cyclase activity.

In the 5 clinical studies (21008, 6253, 6805, 7798, 8297), sponsor enrolled 203 patients seeking pregnancy. The doses used were placebo, 25 IU, 75 IU, 150 IU and 225 IU of Luveris in 41, 19, 100, 13 and 30 patients respectively. 39 patients became pregnant representing 12.2, 5.5, 28.0, 7.7 and 13.3 % of patients in respective treatment groups. Percent spontaneous abortion was similar in placebo and treated groups and % live births were higher in all treated groups. Only one stillborn was reported of the 100 patients treated with 100 IU Luveris.

Luveris was negative in a battery of in-vitro and in-vivo genotoxicity studies. No teratogenic effect was observed in rat and rabbits.

**Safety issues relevant to clinical use:** Based on Luveris structural similarity to u-hLH and p-hLH and the results of the following 5 clinical studies conducted in patients seeking pregnancy, there does not seem to be any concern for its clinical use as proposed.

**Other clinically relevant issues:** none

**Conclusions:** The primary structure of the alfa-chain of r-hLH is identical to that of the alfa-chain of hCG, FSH and TSH and glycoform pattern of the alfa-subunit is closely comparable to pituitary- derived hLH. The B-chain has an N-glycosylation site and its structure and glycosylation patterns are very similar to that of pituitary derived hLH. Sponsor also has an FDA approved h-CG (Ovidrel), which is structurally similar to h-LH and is functionally similar reflected by the fact that both hormones bind to the same receptor. Ovidrel is indicated for inducing final follicular maturation and early luteinization in women undergoing superovulation with follicular stimulating hormone (FSH) prior to IVF/ET. Based on structural similarity of r-hLH with u-hLH and p-hLH and extensive pre-clinical and clinical experience about the safety of the proposed formulation, Pharmacology considers Luveris safe for the proposed indication.

**Communication review:**

Labeling review: No changes suggested for Carcinogenesis, Mutagenesis, Impairment of Fertility or for Pregnancy subtitles.

**RECOMMENDATIONS:** Pharmacology recommends approval of Luveris administered with follitropin alfa under NDA 21-322 as indicated for stimulation of follicular development and ovulation in infertile women with severe deficiency in LH  $\tau$  7

**Internal comments:** none

**External recommendations (to sponsor):** none

**Draft letter content for sponsor (if not same as above):**

**NDA issues:** none

**Reviewer signature:**

**Team leader signature [concurrence/non-concurrence]:**

cc: list:

Original NDA 21=379

HFD-580

HFD-580/A.Jordan/R. Bennett/A.Reddy

**Memorandum of non-concurrence (if appropriate, attached):**

**Addendum to review (if necessary):**

**Studies reviewed within this submission:** Since the main differences between recombinant and natural products, both urinary and pituitary origin are that natural hLH glycans contain N-acetylglucosamine residues and their sulfated derivative while r-hLH glycans contain only sialylated species, which have little relevance to biological activity of the molecule, the studies submitted in this submission are reviewed and summarized briefly.

**Studies not reviewed within this submission:** The following studies which were reviewed on April 12, 1994 by Dr. Steigerwalt under IND 44,108 submission dated December 10, 1993 are not reviewed. Copy of the review is attached.

- GF5315: Efficacy of r-hLH as an ovulatory stimulus
- \ 910568: One-month I.V. toxicity in rats
- \ 910570: One-month S.C. toxicity in rats
- \ 910569: One-month I.V. toxicity in monkeys
- \ 910571: One-month S.C. toxicity in monkeys
  
- Miscellaneous toxicology studies
  1. \ 910572: single dose toxicity in rats, i.v. and s.c.
  2. \ 910573: single dose toxicity in monkeys, i.v. and s.c.
  3. \ 910564: dose-range finding in rats, i.v. 14 days
  4. \ 910566: dose-range finding in rats, s.c. 14 days
  5. \ 910565: dose-range finding in monkeys, i.v. 14 days
  6. \ 910567: dose-range finding in monkeys, s.c. 14 days
  
- Genetic toxicology studies
  1. GF5742: Bacterial mutation test
  2. GF5740: micronucleus test mouse bone marrow
  3. GF5743: mutagenicity in V79 Chinese hamster lung cells
  4. GF5741: in vitro chromosomal aberration
  
- Miscellaneous pharmacology studies
  1. GF5434: r-hLH receptor binding affinity
  2. SRN17/921343: evaluation of effects on the CV system and on the respiration in the anesthetized dog
  3. \ 920699: local irritation study in rabbits by the intramuscular route
  4. GF 5978 (ICRS 92/002): antigenicity and immunogenicity studies of r-hLH using mouse and guinea pig
  
- Pharmacokinetics

Following conclusions were drawn from the above studies:

1. Toxicology studies support the conclusion that r-hLH is well tolerated at doses 1000-fold (IU/kg basis) or greater than those planned for the clinical study. On an IU/m<sup>2</sup> basis, the maximum multiple fully tested in toxicity studies was 333X for monkeys and 167X for rats.

2. r-hLH was effective as an ovulatory stimulus in monkeys. Slight liver hyperplasia and elevation of liver enzymes were noted in some rats and monkeys at doses greater than 2000 IU/kg. In the absence of histology data, it could not be determined if the liver involvement was a dose-related phenomenon and to what extent liver damage may be induced by high doses of this agent.
3. r-hLH exhibited little local irritation in a rabbit study examining a single i.m. injection. Injection sites in the toxicology studies (s.c.) indicated some local inflammation that appeared to be dose-related. These were relatively mild and disappeared during the 2-week withdrawal period. r-hLH was mildly antigenic under conditions stressing allergic reactions. The SC route appeared to be somewhat more effective than i.v. route at inducing neutralizing antibodies, expected in a heterospecific test strain. However, since the carbohydrate composition of the recombinant glycoprotein differs from natural product, there is no guarantee that this response will be diminished or absent in human studies.
4. A confounding factor in PK studies was the production of neutralizing antibodies, which may have been responsible for some of the variability noted in the data collected. There were no indications of accumulation of the test article.
5. r-hLH was found to be negative in the Ames assay, V79 Chinese hamster lung cell assay, cultured human lymphocyte assay and in the mouse bone marrow micronucleus test.

**Introduction and drug history:** As given under Overall Summary and Evaluation

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## PHARMACOLOGY:

### Primary pharmacodynamics:

Mechanism of action: Luveris administered concomitantly with r-hFSH stimulates development of a competent follicle and indirectly prepares the reproductive tract for implantation and pregnancy.

Drug activity related to proposed indication: Induction of ovulation in infertile women with severe LH and FSH deficiency.

**Secondary pharmacodynamics:** Characterization of r-hLH in vitro and in vivo demonstrated that:

- 1) the receptor binding and displacement in the RIA for r-hLH, u-hLH, hMG or hCG showed similarity in binding to and displacement characteristics using the corpus luteum LH receptors,
- 2) the immunoreactive and bioactive serum clearance half life in monkeys of 48 and 123 minutes, respectively for r-hLH were in good agreement with those of p-hLH of 65 and 141 minutes, respectively,
- 3) increase in testosterone production by r-hLH in mouse Leydig cells vitro paralleled those by hMG confirming that the appropriate post-receptor effects followed the binding to the LH receptor,
- 4) increased progesterone production by r-hLH in both rat and monkey luteal cells in vitro over baseline paralleled those of hMG and HCG, confirming that the binding to the LH receptor was followed by the appropriate post-receptor effects,
- 5) graded dose of recombinant and natural hLH preparations tested provided similar increases in rat seminal vesicles and ventral prostate weights,
- 6) 25 IU of hMG, r-hLH and u-hLH all caused a significant increase in progesterone secretion within 60 minutes of iv injection,
- 7) a single administration of r-hLH and h-CG both induced ovulation in 90% of the follicle-stimulated does. However, r-hLH in contrast to hCG produced a greater percentage of good quality embryos and a better implantation rate,
- 8) the development and function of corpora lutea and thus induced periovulatory events were similar after a single injection of r-hLH or p-hLH in rhesus monkeys. The terminal half life of r-hLH was similar to p-hLH,
- 9) follicular growth in LH deficient monkeys was more rapid in the presence of r-hLH + r-hFSH than with r-hFSH alone, indicating that LH and FSH act in synergy to promote follicular growth. Also estradiol secretion was 4-fold in the presence of LH. It was stated that an FSH:LH ratio of 1:1 is not optimal,
- 10) r-hLH binds to Leydig cell tumor cells (MA-10) receptor with slightly greater affinity than p-hLH.

**Pharmacology conclusions:** On pharmacodynamic basis r-hLH, u-hLH, h-MG or hCG had similar effects.

## **SAFETY PHARMACOLOGY:**

### **Neurological effects:**

Central nervous system: using doses of 0, 200, 2000 and 20000 IU/kg no effect was seen on spontaneous locomotor activity, sleeping time induced by pentobarbital in mice. No effects of r-hLH were observed on the convulsive effects of pentetrazol or on convulsive effects of electroshock. No analgesic activity at any dose levels in mice and no effect on body temperature in rats.

Autonomic nervous system and smooth muscle: using dose levels of 0, 0.1, 0.4 and 1.6 IU/ml of r-hLH, no change was observed in the resting potential of the guinea pig ileum in vitro. Using single iv dose of up to 20000 IU/kg did not induce significant alterations of the motility pattern of the uterus in the rat.

**Cardiovascular effects:** Intravenous administration of increasing doses (0, 20, 200, 2000, 20000 IU/kg) 60 minutes apart in male and female anesthetized dogs (2/s) did not significantly affect arterial pressure, heart rate, cardiac function, respiration or blood flow. It was stated that statistically significant changes in ECG lead II waveform intervals were considered devoid of pharmacological significance.

**Pulmonary effects:** Doses used for cardiovascular effects had no effect on respiration

**Renal effects:** none mentioned

**Gastrointestinal effects:** In mice SC administration of 0, 200, 2000 or 20000 IU/kg had no effect on gastrointestinal motility.

**Abuse liability:** none described

**Other:** Recombinant gonadotropins (r-hCG, r-hLH or r-hFSH) at doses of 0.1, 1 and 10 IU/ml incubated in vitro for 48 hours with human ovarian cancer cells (Caov-3 and SK-OV-3) did not affect cell proliferation when tested in serum-free or low-serum medium, suggesting that recombinant gonadotropins do not stimulate oavry cancer growth.

**Safety pharmacology conclusions:** r-hLH had no adverse effects on central nervous system. It had no effect on blood pressure, heart rate, blood flow, respiration or GI motility.

## **PHARMACOKINETICS/TOXICOKINETICS:**

**PK parameters:** PK in rat after single and repeated dosing is shown in table below:

Parameter	Single dose		Repeat dosing
	i.v	s.c	
Cmax IU eg/l	1144	116	180
AUC h.IU eg/l			
0-72 h	2838	1752	
0-infinity	2839	1815	
24 hr	2942		2751
T1/2 hr	24	22	48

Single dose was 63 IU/kg and multiple dose was 63 IU/kg for 14 days.

In monkeys single escalating dose was used. It was 10, 63 and 400 IU/kg by the I.V. route and 400 IU/kg by the I.M and S.C route given in a cross over design (I.V. to S.C. and S.C. to I.M.)

PK was linear from 63 to 400 IU/kg but not between 10 to 63 IU/kg. T1/2 after I.M. and S.C. was less than one hour. Mean bioavailability was 0.61 for I.M. and 0.48 for S.C.

The PK profiles following r-hLH, p-LH and hMG at 400 IU/kg was similar with T1/2 of 11.0, 10.2 and 9.1 hours, respectively.

Repeat dose of 63 IU/kg SC or IM for 7 days resulted in no apparent accumulation of r-hLH. IM showed greater bioavailability

**Absorption:** Absorption was quicker in monkeys compared to that in the rat

**Distribution:** small amount due to r-hLH radioactivity increased form 3-6 hours after administration in ovaries and testes indicating these as the target organs in the rat Radioactivity greater than in plasma was observed in kidneys, stomach and target organ (ovary) at all times.

Major concentration of radioactivity in monkeys was observed in thyroid, GI tract and kidneys. Radioactivity conc was higher than plasma in ovaries (1-16 hours), pituitary (6-24 hours) and mammary gland (at 24 hour)

**Metabolism:** Plasma SDS showed beta-subunit at 3 and 6 hours. By gel filtration free I<sup>125</sup> at all sampling times. In liver and kidneys majority of radioactivity was as free I<sup>125</sup>. Urine and bile also had free iodine 125.

**Excretion:** radioactivity was mainly in the urine. In rats, it amounted to 84% and 87% after iv and sc administration during 168 hours after administration. 10% and 6% was recovered in feces. Biliary excretion by both routes up to 8 hours after injection was 3-5%. Milk/plasma ratio was 1.26, 2.56, 7.10 and 3.08 after 3, 6, 16 and 24 hours, respectively. In monkeys 92-103% was excreted in urine and 3-4% in feces.

**Other studies: -**

#### TOXICOLOGY:

Single dose toxicity studies, dose-range finding studies for up to 14 days and one month toxicity studies in rats and monkeys by the i.v. and s.c. routes were reviewed under IND 44,108 on 4-12-1994. These are summarized under Studies not reviewed within this submission section.

Only following 2 additional toxicity studies submitted in the NDA

1. \ 1930152: 13-week repeated dose in rats administered by sc with six month recovery. Dose used were 0, 10, 100, 1000 IU/kg/day. 20 females/g
2. \ 930153: 13-week repeated dose in monkeys administered by sc with six month recovery. Doses used were 0, 10, 100, 1000 IU/kg/day. 6 females/g

Significant findings in the rat toxicity study were swelling of nipples in groups 3 and 4 during second half of treatment. The body weight and food intake of group 4 animals was increased. Virtually all treated animals exhibited anti-LH antibodies from week 6 of treatment period. Antibody formation resulted in significantly reduced AUC. At the end of treatment period, LH levels were undetectable. r-hLH treatment caused dose-dependent increase in estradiol levels. All observed treatment-related changes were seen to revert in recovery animals. Follicle cysts still persisted in groups 3 and 4 and anti-LH antibodies generally persisted.

In monkeys swelling of external genitalia was confined to a single group 3 animal from second week and was still present at end of recovery period. Histology revealed some perivasucular mononuclear cell cuffing at injection site in group 4 animals. Dose-dependent relationship was observed between r-hLH treatment and antibody production in group 2, 3 and 4 animals. For groups 3 and 4, significant reduction of AUC was observed after 38<sup>th</sup> administration. At the end of treatment period, LH serum levels were almost undetectable. No correlation between r-hLH treatment and estradiol and progesterone levels was observed. All treatment-related effects reverted upon recovery except levels of anti-LH antibodies, which remained at the same levels at end of treatment period.

**Histopathology Inventory for NDA #**

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				

Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed

\*, organ weight obtained

### GENETIC TOXICOLOGY:

As reviewed and report under IND 44,108 dated 4-12-1994, r-hLH was not mutagenic in the in-vitro mutagenicity studies (bacterial mutation, mutagenicity in V79 Chinese hamster lung cells, in vitro chromosomal aberration assays) or in vivo mouse micronucleus assay.

**Genetic toxicology conclusions:** r-hLH did not exhibit genotoxic potential

**Labeling recommendations:** none

### CARCINOGENICITY:

None submitted

### REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

The following reproductive toxicity studies were conducted at  $\downarrow$   
 $\downarrow$  in accordance with OECD-GLP guidance.

1.  $\sim$  Exp. No. 930011: Preliminary reproductive toxicity studies in  $\sim$  CD (SD) BR female rats of the test article r-hLH administered by subcutaneous route at the doses of 0, 5, 50, 500 IU/kg/day

In this study test article was administered in different periods of the reproductive cycle (pre-mating to until successful copulation-Exp 931011; from day 0 to day 7 of gestation- Exp. 932011; from day 7 to day 17 of gestation-Exp. 933011 and from day 17 of gestation to day 21 of lactation-Exp. 930011) in order to define the experimental design and the dosages for the main studies.

The dose of 5 IU/kg/day in normal saline had no adverse effect on reproduction when given in different periods of the reproductive cycle.

Doses of 50 and 500 IU/kg/day induced impairment of reproductive capacity such as inhibition of mating when given in the pre-mating period, resorptions when given in the pre-implantation or in the organogenesis period, and difficult and prolonged parturition with early death of pups when given in the late pregnancy and lactation.

Based on these findings, doses of 5, 10 and 20 IU/kg/day were selected to be used in the main Segment 1,2 and 3 studies in rats.

2.  $\backslash$  Exp No. 930151: Preliminary teratogenesis study in New Zealand White rabbits of the test article r-hLH administered by subcutaneous route at doses of 0, 5, 50, 500 IU/kg/day

In this study test article administration to pregnant rabbits from day 6 to day 18 of gestation induced effects on reproduction (increase of resorptions) at 50 and 500 IU/kg/day while no apparent effects were observed at 5 IU/kg/day. Based on this, doses to be used in the main teratogenesis study were selected as 5, 10 and 20 IU/kg/day.

3.  $\backslash$  Exp No. 930654: Fertility and reproduction study in  $\backslash$  CD (SD) BR female rats of the test article r-hLH administered by subcutaneous route at the dosages of 0, 5, 10, 20 IU/kg/day

In this study 24 female rats/group were treated for 14 days before the start of the mating period through gestation day 7. Presence of spermatozoa in the vaginal smear was considered day 0 of gestation. The females with positive vaginal smear were caesarian sectioned on day 20 of presumed gestation. Maternal and fetal parameters were recorded.

Treatment induced a lower fertility index at the dosage of 20 IU/kg/day, with an increase of pre- and post-implantation losses and a lower fetal weight. An increase in pre- and post-implantation losses was also found at 10 IU/kg/day. The no observed effect dose level was considered 5 IU/kg/day for both dams and their conceptuses. Although few fetuses were available for examination, no malformed fetuses were observed even at the high dose of 20 IU/kg/day.

4. \ Exp. No. 930652: Teratogenesis study in \ CD (SD) BR rats of the test article r-hLH administered by subcutaneous route at the dosage of 0, 5, 10, 20 IU/kg/day

In this study 40 females were used per treatment group. 25 were assigned to caesarean section on day 20 of presumed gestation and 15 were allowed to deliver spontaneously and were sacrificed when F1 pups were weaned on day 21 of lactation.

An increase in early resorptions and post-implantation losses were observed at 10 and to a greater extent at 20 IU/kg/day. In the 20 IU/kg/day group, 5/21 had 100% resorptions. As a consequence a decrease of live fetuses was seen at 10 and 20 IU/kg/day. In these groups there was decreased ossification of the head and gravid uterus weight and litter weight were also lower than those of the controls. No drug-related malformed fetuses were found.

No differences were observed in the viability index on day 4 or in the weaning index among the different experimental groups showing that the postnatal survival was unaffected.

No significant effects were found in the morphological, physical or behavioral development of the F1 pups or in the F1 reproductive performance.

The NOAEL is considered 5 IU/kg/day for both dams and conceptuses.

5. \ Exp. No. 930655: Teratogenesis study in New Zealand White rabbits of the test article r-hLH administered by subcutaneous route at the dosage of 0, 5, 10, 20 IU/kg/day.

20 mated females with positive smear were used. On day 29 of gestation, the females were killed and pregnancy and litters parameters were determined. Live fetuses were examined for external abnormalities and macroscopically examined for internal organs. Fetuses were processed for visceral and skeletal abnormalities.

There were no clinical signs of local reactions, behavioral changes or drug-related deaths. Body weight gain for the 20 IU/kg /day group was lower than that of control group.

An increase of early resorptions and of post-implantation losses was found in 10 and 20 IU/kg/day treated groups with related decrease of viable fetuses.

One plurimalformed fetus was found at external examination of 52 viable fetuses in the 20 IU/kg/day group (litter No.70). This was described as incidental. There were no other teratogenic findings at skeletal and visceral examination.

The NOAEL was considered 10 IU/kg/day for general toxicological effects on the does and 5 IU/kg for the effects on reproduction.

6. \ Exp. No. 930653: Peri- and postnatal study in \ CD (SD) BR rats of the test article r-hLH administered by subcutaneous route at the dosage of 0, 5, 10, 20 IU/kg/day

Twenty-five female rats/group were treated from day 17 of gestation through day 21 of lactation. All F0 females were allowed to deliver spontaneously. Selected animals of F1 generation were reared without treatment to maturity and tested for reproductive ability.

F0 generation: no clinical signs, local reaction, behavioral changes or deaths were observed. The parturition was unaffected although gestation was shorter in the 20 IU/kg/day group compared to that of the control group. A dose-related increase in stillborn pups and a related decrease of live pups were observed in the 10 and 20 IU/kg/day treated groups. Also post-natal survival of pups in these groups was lower.

F1 generation: As for F0 generation no clinical signs or behavioral changes or drug-related mortality was observed.

No differences were observed in the motor coordination, in memory and recall ability (Water Y Maze) and in the motor activity in the Open Field test between treated and control group. The testes descent and the vaginal opening of the 10 and 20 IU/kg/day groups was delayed slightly compared to control group. The mean body weight of the F1 males and females in the 10 and 20 IU/kg groups was lower than that of the control group.

No effects were observed on the F1 gestation parameters. One malformed fetus with fore limb reduced size was reported in the 5 IU/kg group and one fetus with ansarca and one with umbilical hernia were found in the 10 IU/kg/day group. No malformed fetus was found in the 20 IU/kg/day treated group. It was stated that malformations found are not uncommon in the \ colony data. Testes and ovary weights of the F1 parent animals in the 10 and 20 IU/kg dose groups were lower in comparison to those of the control animals. As such an effect on the reproductive performance at 20 IU/kg/day could not be excluded.

The NOAEL was considered to be 10 IU/kg/day for general toxicological effects on the dams and 5 IU/kg for the effects on offspring.

**Reproductive and developmental toxicology conclusions:** r-hLH was not teratogenic in the rat and rabbit segment 2 studies.

**Labeling recommendations:** none

**SPECIAL TOXICOLOGY STUDIES:**

Immunogenicity studies in mice and guinea pigs demonstrated limited r-hLH induced allergic reactions. Severe symptoms of anaphylaxis were rare in guinea pigs administered r-hLH and no mice showed detectable concentrations of specific IgE.

Sensitization observed after parenteral challenge in guinea pig was attributed to r-hLH being a heterologous protein to guinea pigs.

Local irritation studies in rabbits by the i.m. and s.c. routes demonstrated that r-hLH preparations are well tolerated.

**ADDENDUM TO REVIEW:**

(if necessary)

**APPENDIX/ATTACHMENTS:**

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Krishan L. Raheja  
2/8/02 10:36:28 AM  
PHARMACOLOGIST

Alexander W. Jordan  
2/11/02 07:58:06 AM  
PHARMACOLOGIST

NDA 20-322

Luveris™ (lutropin alfa for injection) 75 IU

Serono, Inc.

**Pharmacology/Toxicology review(s) and Memoranda**

This drug product has been approved in higher dosages. A Pharmacology review is not required for this supplement.

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