CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-149

PHARMACOLOGY REVIEW

NDA 21-149
Ovidrel

9/14/00

Pharmacology Team Leader Labeling Memo

I have reviewed the label of 9/13/00 and the pharmacology sections are satisfactory.

/S/ 9/18

Alex Jordan, PhD

NDA 21-149
HFD-580

NDA 21-149
Serono Laboratories

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: recombinant human choriogonadotropin, IVF, ART
Karen Davis-Bruno; Ph.D.
Division of Reproductive and Urologic Drug Products/HFD#580
Review Completion Date: 4/12/00

NDA 21-149
Serial number/date/type of submission: NDA submitted 11/26/99
Information to sponsor: Yes (X) No ( )
Sponsor: Serono Laboratories; Norwell, MA
Manufacturer for drug substance: Laboratoires Serono; Aubonne, Switzerland
Industria Farmaceutica Serono; Bari, Italy
Serono Laboratories; Randolph, MA

Drug:

Code Name: r-hCGα

Generic Name: recombinant human choriogonadotropin alpha

Trade Name: Ovidrel

CAS Registry Number: CAS-177073-44-8 (alpha subunit CAS-56832-30-5; beta subunit CAS-56832-34-9)

Molecular Formula/ Molecular Weight: [redacted]

Structure: choriogonadotropin alpha consists of two non-covalently linked subunits (α,β) consisting of 92 and 145 amino acids respetively with carbohydrate moieties linked to ASN-52 and ASN-78 (α subunit) and ASN-13, ASN-30, SER-121, SER-127, SER-132 and SER-138 (β subunit).

Relevant INDs/NDAs/DMFs: IND 48,934

Drug Class: gonadotropins (recombinant, human). Human choriogonadotropin is produced by trophoblasts by post conception Day 6, and stimulates both corpus luteum (CL) and early fetal-placental endocrine function. In early pregnancy hCG prolongs the life of the CL activating the secretion of estrogen and progesterone until this function is provided by the placenta. Choriogonadotropin alpha binds to the LH/hCG receptor of the granulosa and theca cells of the ovary to effect these changes in the absence of an endogenous LH surge. Placental and human pregnancy derived urinary hCG are glycoproteins which belong to the same hormone family.

Indication: induction of final follicular maturation and early luteinization in women [redacted] follicle stimulating hormone (FSH) [redacted] assisted reproductive technology [redacted] (ART)

Clinical Dose: 250 μg (5000 USP IU units) to [redacted] one day following the last dose of the follicle stimulating agent

Drug Product: lyophilized r-hCG 285 µg ——— (includes excess added to assure delivery of 250/500 µg); reconstituted in 1 ml sterile water for injection
Excipients: sucrose 30 mg, phosphoric acid 0.98 mg, sodium hydroxide q.s. (pH adjustment

Route of administration: subcutaneous

Proposed clinical protocol or Use: Ovidrel is intended for induction of final follicular maturation and early luteinization in infertile women, appropriately pretreated with FSH as part of ART

Previous clinical experience: HCG has been widely used in the treatment of male and female infertility. The sponsor has developed Ovidrel to replace u-hCG which is derived from urine of pregnant women and is approved in the USA for the same indication. The safety/efficacy of Ovidrel was examined in two clinical studies for ART (USA. Europe/Israel). The primary efficacy assessment was the number of oocytes retrieved/treated patient.

Introduction and drug history: All preclinical studies have been reviewed in IND 48,934
PHARMACOLOGY:
Mechanism of Action Related to Proposed Indication: Mimics an LH surge after FSH-induced follicular development and induces:

1. Oocyte maturation: re-initiates oocyte meiosis arrested at prophase I allowing the ovulation of a metaphse II (mature) oocyte.
2. Cumulus oophorus maturation: cells undergo mucification allowing the oocyte and cumulus to leave the ovary and reach the fallopian tube at the time of follicular rupture.
3. Follicular rupture
4. Corpus luteum formation: Ovidrel stimulates granulosa and theca cell production of progesterone

Based on these effects, Ovidrel can be used to :

1. induce final follicular maturation and trigger ovulation in anovulatory women
2. for assisted reproductive technologies (ART)
3. to support the luteal phase

Bioassays of uterus, seminal vesicle or prostate weight gain in rats were used to determine bioactivity. These bioassays are based on the stimulation of steroidal secretion from LH/CG receptor expressing cells. Receptor binding studies add further support by demonstrating that r-hCG and u-hCG bind to the LH/CG receptor with similar affinities. R-hCG, u-hCG and a USP standard had equivalent bioactivity, establishing bioidentity.

The ability of r-hCG to induce ovulation was examined in a dose ranging study in macaques where the optimal duration (>48 h) and amplitude of the gonadotrophin surge required to stimulate ovulation was determined. Administration of 1000 IU of r-hCG or u-hCG yielded a

high amplitude and long duration gonadotrophin surge resulting in 80-100% fertilizable oocytes and ~50% fertilization rate. Lower doses of r-hCG resulted in 50-60% fertilizable oocytes and a lower fertilization rate (25-34%). Administration of 2500 IU r-hFSH resulted in 100% of macaques yielding fertilizable oocytes, although 40% of the animals yielded only one fertilizable oocyte/animal. The fertilization rate was 47%.

The ability of r-hCG to rescue luteal progesterone and relaxin production was evaluated in Rhesus monkeys under conditions of simulated early pregnancy. Relaxin in combination with progesterone is thought to inhibit spontaneous uterine contractility during early pregancy. The rise in circulating relaxin during early pregnancy is a nonsteroidal marker for *in vivo* bioactivity of CG. U-hCG and r-hCG were equivalent in stimulating the increased ovarian steroidogenic and peptidergic output which occurs during early pregnancy. The levels and pattern of progesterone and relaxin were similar. The administration of a 3b-hydroxysteroid dehydrogenase inhibitor (trilostane) abolished circulating progesterone without altering relaxin concentrations. This suggests that progesterone is not a local mediator of hCG-stimulated ovarian relaxin production or release during early pregnancy.

The bioactivity of r-hCG in MA10 Leydig cells demonstrates no major differences between the recombinant and natural origin in the in vitro assay.

The incidence of ovarian cancer increases with age, particularly at menopause. The age related increase in the levels of circulating FSH and LH have been postulated to contribute to the incidence of ovarian cancer. Epidemiological data from infertility therapy shows an increased risk of ovarian cancer by long treatment with clomiphene (estrogen antagonist) without a correlation with the use of gonadotropins. The potential growth promoting activity of r-hCG, r-hFSH and r-hLH on ovarian cancer was evaluated *in vitro* by a proliferation assay based on ^{3}H-thymidine uptake in human ovarian cell lines. Recombinant gonadotropins do not affect the growth of ovarian cancer cell lines when tested up to

SAFETY PHARMACOLOGY:

Cardiovascular/Respiratory effects: Effects of r-hCG on BP, ECG, HR and respiration were examined in anesthetized rats and beagle dogs. No effects were observed in rats at doses up to 18800 IU/kg or dogs up to 2000 IU/kg. Increased respirations were noted in one female dog at 20000 IU/kg.

PHARMACOKINETICS/TOXICOKINETICS:

Comparison of r-hCG and u-hCG in Monkey: Six male monkeys were treated with a single IV biologically active dose of 100 IU/kg of r-hCG and u-hCG. The t1/2 is slightly higher for u-hCG with an $AUC_{0-\infty}$=24000±3000 IU h/land $AUC_{0-\infty}$=16000±1000 for r-hCG.

Repeat Dose PK in Monkey: Six male cynomolgus monkeys were treated daily for with 100 IU/kg of r-hCG (120 IU/kg immunoreactive dose) given SC for 7 days.

Day 1	
Cmax	400±70 IU/l
Tmax	4±1 h
$AUC_{0-\infty}$	10,000±2000 IU h/l
Day 7	
Cmax	900±100 IU/l
Tmax	5±1 h
AUC_{0-24}	13,000±2000 IU h/l
AUC: Day 7/Day 1	1.3±0.2
T1/2 (terminal)	24±3

Comments: A population PK model was developed to assess TK for r-hLH and r-hCG. However the small numbers of animals (6-12) precluded the sponsor from further evaluation of the model.

The ADME reported is based on h-LH studies which is structurally similar to h-CG and both share the same receptor. Serono has performed experiments for Lutropin alfa which they consider supportive an ADME rat study suggested that ^{125}I-rLH was excreted 84% in urine by the IV route and 87% by SC dosing. The amount excreted in the feces was 10% and 6% respectively. Urinary excretion occurred during the first 24 h, whereas fecal excretion was almost complete within 48 h. Biliary excretion for either IV or SC route was 3-5%, primarily as an acid soluble material. The concentration of radioactivity in milk was similar to the plasma (milk/plasma=1.15±0.57). Thereafter the relative amount in milk/plasma increased up to 7.1±4.09 at 16 h post dose. By 24 h, the level of r-hLH in milk had decreased but was still greater than that in plasma (milk/plasma= 3.08±1). The plasma profile was similar to that found in pregnant females and was characterized by a peak level at 3-6 h and a rapid decline between 6-16 h.

TOXICOLOGY:

Acute: Single dose studies in rats (SC and IV) given 2000, 20,000, 200,000 IU/kg were observed for 14 days. Testis weight was decreased in all groups unrelated to dose. A decrease in spermatogenesis, associated with sperm degeneration and tubular vacuolization was observed. High doses of h-CG (e.g. 200,000 IU/kg) have been shown to over stimulate Leydig cells resulting in elevations in androgen secretion which feedback to inhibit FSH release from the pituitary resulting in decreased spermatogenesis and germ cell degeneration in rats but not in primates or humans. In females a slight increase in the frequency of follicular cysts in all treated groups was observed compared to controls. An increased number of corpora lutea were observed in rats given SC doses.

Single dose studies were performed in cynomolgus monkeys (2/sex) via SC and IV administration at 200,000 IU/kg of r-hCG with a one week washout between testing dosing routes. Post mortem exam two weeks post dose demonstrates ovarian stimulation (follicular hematocyst) in one female. Changes were not observed at the injection sites. Antibodies were detected in 2 males and 1 female 14 days after first dosing and in one female 35 days after first dosing.

Subacute: One month dosing in rats (4/sex/dose) by SC and IV routes at 20, 200, 2000, 20,000 IU/kg/day induced reproductive effects in males and females which were comparable to those observed with LH. In males serum testosterone increased dose dependently with IV dosing at all doses. Testosterone increased at doses up to 200 IU/kg/day with SC administration, however higher doses did not result in further increases. There was a slight decrease in size and weight of testes with slight to marked decreased spermatogenesis at 20 IU/kg. Germinal cell degeneration, interstitial cell hyperplasia was induced at all doses. An increase in size and weight of prostate and seminal vesicles was seen at ≥20 IU/kg SC or ≥200 IU/kg IV with associated epithelial hyperplasia. A decrease in thymus weight and size was associated with atrophy in all SC groups and from 200 IU/kg given IV in a dose related manner.

Estradiol levels increased in females in a dose related manner from 200 IU/kg/day. Mammary glands showed slight to moderate acinar and ductal dilation, sometimes associated with secretion. Kidney weight tended to increase with all IV doses and with the highest SC dose, without associated histology. The sponsor did not explain why SC dosing was more effective in increasing prostate/seminal vesicle and decreasing thymus weight although less effective in increasing kidney weight. In females ovarian weight was increased in all treated groups with increased size and number of corpora lutea and an increase in follicular cysts that were sometimes hemorrhagic. Mucosal hyperplasia was reported in uterus and vagina at >200 IU/kg/day. A dose related increase in pituitary weight and size characterized by basophilic hypertrophy and increased vacuolation was observed (except in low IV doses).

In both sexes a decrease in size and weight of adrenal glands was seen in high dose SC groups and all IV dose groups with atrophy of the zona fascicularis and hypertrophy of zona glomerulosa. Thymus atrophy and hepatocellular hypertrophy were seen in SC groups given ≥200 IU/kg IV, this was attributed to the increase in estrogen induced by r-hCG. The differential effects of these routes are not explained. Injection site inflammation was occasionally seen in rats at the highest dose.

A one month study in cynomologus monkeys (4/sex/group) given 20, 200, 2000, 20000 IU/kg/day were necropsied (3/sex/group) at the end of four weeks (1/sex/group given an additional 4 week recovery. Testosterone levels were increased in males at all dose levels by both routes. Estradiol was below the detection limits in all females for both routes, which differs from the rats. Increased number of corpora lutea, consistent with h-CG ovarian stimulation was observed at the highest dose given SC. In males, a dose related increase in prostate and seminal vesicle weight was observed. Testis weight was increased at the highest dose by the SC route only. Thymus weight was decreased with dose related thymic atrophy. Glandular epithelial hypertrophy and dilation in the prostate and seminal vesicles was noted at all dose levels. Dose related both routes induced testicular interstitial hyperplasia with accelerated spermatogenesis in monkeys given the highest dose, SC.

Females had decreased thymic weight at the highest dose, SC with associated atrophy and an increase in uterine and ovarian weight. Both routes at the highest dose increased the number of corpora lutea. Endometrial hyperplasia was noticed in one female treated SC at the highest dose. Mild inflammation was present at the injection site.

Chronic: A 26 Week SC toxicity study in male cynomolgus monkeys given 0, 50, 500, 5000 IU/kg/day was compared with u-hCG in 5/group. An increase in body weight of 27%, 20%, 55% in treatment groups respectively, was observed. A similar increase was observed for u-hCG (28%) compared to controls (17%). Antibodies were detected by Week 4 in 2/5, 5/5, 3/5, 5/5 for Groups 2-5 respectively. By Week 12 and 26, antibodies were detected in serum of all monkeys at all dose levels of r-hCG and at 500 IU/kg/day of u-hCG. Testosterone levels increased from 3

ng/ml baseline to 60 ng/ml at Week 4 in all treated groups. Continuation of treatment to Week 12 and 26, demonstrates observed testosterone levels returned to baseline with high antibody titers present. Absolute testes and seminal vesicle weights were observed in the high dose r-hCG and u-hCG groups with pituitary weight increased in all treated groups. Relative weights were similar to control except seminal vesicles of u-hCG treated monkeys. The frequency of SC hemorrhage at the injection site was increased in the 500 and 5000 IU/kg/day. A dose related increase in frequency and degree of perivascular mononuclear cell cuffing was observed at the injection site in all r-hCG treated groups compared to controls. Prolactin secreting pituitary cells showed slight to moderate hypertrophy, which was dose related in frequency and degree in all r-hCG treated groups. Mammary gland acinar hyperplasia was seen in the high dose groups. U-hCG induced similar modification to r-hCG. A NOAEL was established at 5000 IU/kg of r-hCG.

OVERALL TOXICOLOGY SUMMARY:

Toxicology studies support the safety of r-hCG in monkeys given 5000 IU/kg for 26 weeks and in rats given 20 IU/kg for one month. Generally the findings reflect the expected pharmacologic effects on target organs. The testicular changes are seen in rodents at 200 IU/kg (HED=32 IU/kg). Adolescent rats require sufficient pituitary gonadotropins and testosterone (Leydig cell derived) for spermatogenesis (FSH stimulation of Sertoli cells). Inhibition of FSH induced by hCG is considered responsible for the decreased spermatogenesis and germ cell degeneration seen in treated rats. The increased prostate and seminal vesicle weight is consistent with elevated levels of testosterone induced by r-hCG. These male reproductive effects are opposite to those induced in primates or observed clinically with u-hCG (Profasi).

Species Treatment		Cmax (IU/L)	Multiple of human
Monkey 26 Wk. NOAEL=5000 IU/kg	Dose 1	25860±3907	~200
	Dose 178	62,342±73,404	
Human 250 µg, SC		124±42	--

CARCINOGENICITY: Studies were not submitted for the following reasons:

1. Clinical indication is not for chronic/prolonged use
2. R-hCG is a glycoprotein biologically identical to endogenous hCG and u-hCG
3. R-hCG was not genotoxic or clastogenic in a battery of mutagenicity tests and did not result in any suspicious changes in tissues of animals subjected to testing up to 26 weeks (monkey)
4. Repeat dosing in rats demonstrate that r-hCG causes hormonal effects on male gonads which are opposite to those induced in primates and expected in clinical use based on the experience gained with urinary h-CG (Profasi).
5. Rats develop anti-hCG antibodies within 4 weeks of treatment in subchronic toxicity testing
6. There is no evidence that excessive, long duration secretion of hCG, as in trophoblastic tumors or in teratomatous chorionic tumors is associated with increased tumor incidence. Increased tumor incidence has not been reported following years of treatment with hCG for hypogonadotropic hypogonadism and cryptorchidism.
7. A cell proliferation assay using r-hCG, r-FSH and r-hLH _____ on ovarian tumor cell growth demonstrates an inability of gonadotropins to stimulate growth.

IMMUNOTOXICOLOGY: Neutralizing antibodies to r-hCG were induced in rat and monkey toxicity studies following <2 weeks dosing, SC. This reduced the serum concentration of r-hCG and testosterone as determined by immunoassay.

REPRODUCTIVE TOXICOLOGY: Therapeutic treatment with hCG in women for ovulation induction requires a single injection on a few occasions. In males, restoration of testosterone production and spermatogenesis for hypogonadotropic hypogonadism requires up to several months administration. Reproductive toxicity information was provided in pregnant females for embryo-fetal toxicity (Acta Endocrinologica 112:586-594, 1986). Male fertility was assessed as part of the toxicology studies.

Males: One month repeat dose toxicity studies in rats (SC, IV) show a decrease in size and weight of testes consistent with decreased spermatogenesis and germinal cell. These testicular changes are known effects of hCG in rodents due to inhibition of FSH and is considered responsible for the decreased spermatogenesis and germ cell degeneration of the testes. These findings are opposite to those induced in primates where repeat dose toxicity studies sometimes show acceleration of spermatogenesis in young adult monkeys and sperm analysis in adult monkeys did not show adverse effects. Testosterone was increased as a result of hCG stimulation of Leydig cells. U-hCG has been used clinically for decades to restore testosterone production in hypogonadotropic hypogonadism and for cryptorchidism.

Females: The effects of hCG (500 IU/day) given SC administered from Day 1-5 of rat pregnancy (pre-implantation), Day 8-11 (post-implantation), Day 13-16 (late pregnancy) are summarized:

Pre-implantation: hCG reduced implantation sites (29-41%) compared to control and markedly increased serum progesterone.

Post implantation: hCG caused 50-55% fetal death. Serum progesterone and estradiol were increased by 2X compared to control pregnant rats. The sponsor implicates the high estradiol level is responsible for the partial fetal resorption.

Late Pregnancy: H-CG treated rats had vaginal bleeding on Day 24, without parturition (normal Day 22-23) and were sacrificed Day 25. Fetal mortality was 57%. Serum progesterone (2X control on Day 16) was considered responsible for the delay in parturition. In pregnant rats, serum progesterone declines after Day 19. High levels of progesterone impair propagation and uterine contractility.

Summary and Evaluation: The consequences of treating pregnant rat with r-hCG is predictable based on the known pharmacology. Infertility, intrauterine death and impaired parturition were observed at a dose equivalent to 3X the maximum human dose (10,000 USP, IU).

Labeling Recommendations: R-hCG has abortifacient properties when given to pregnant rodents, it adversely affects both fetal survival and growth. Treatment of pregnant women is therefore contraindicated.

GENETIC TOXICOLOGY:

Study#/ Objective	Test system	Strain/cell line	Animals	Route	Treatment duration	Dose	Findings
GF6802 Bacterial Mutagenicity	Bacteria	[redacted]		In vitro	72 h	165 495 1485 4454 13361 (IU/plate)	± S9 negative
GF6803 Mammalian Mutagenicity	V79 Chinese hamster lung cells			In vitro	2h	495 1485 4454 13361 (IU/plate)	± S9 negative, 2 exp.
GF6805 Chromosome aberration in human lymphocytes	Human lymphocytes			In vitro	2.5 h	495 1485 4454 13361 (IU/ml)	± S9 negative
GF6804 Mouse Micronucleus	Mouse	— CD-1(ICR) BR	45M 45 F	Iv	Single dose	2000 20000 2000000 (IU/kg)	Negative

SPECIAL TOXICOLOGY STUDIES:

A local irritation study in rabbits was performed by the IM route. New Zealand White rabbits (6/group) were given 150 µg/ml in the quadriceps femoris muscle on the right side with the left side a saline control. Acetic acid (0.425%, 1.7%) was used as a positive control. Animals were sacrificed on Day 2 (n=3) and the remainder on Day 14. Local irritation of r-hCG was equal or lower than that observed with saline and was reversible.

OVERALL SUMMARY AND EVALUATION:

Introduction: Urinary derived hCG is approved in the USA for the same indications for which r-hCG would be used. R-hCG exhibits similar biological activity as the u-hCG and it is anticipated that r-hCG will be clinically equivalent to u-hCG.

Conclusions: Pharmacology recommends approval of r-hCG for induction of follicular maturation and early luteinization following [redacted] with FSH prior to ART, based upon the safety data provided.

Communication Review:
Labeling Review (NDA): Pharmacology recommends that the sponsor change the submitted label from Pregnancy Category — X based on the reprotoxicity data. [redacted]

RECOMMENDATIONS:

External Recommendations (to sponsor):

A labeling change from Pregnancy Category — X is recommended based upon the reprotoxicity data. Please include the following [redacted]

[redacted] based on body surface area.

genotoxicity AS

The "Carcinogenicity, Mutagenicity, Impairment of Fertility" section should be amended to include the following: In vitro ~~mutagenicity~~ testing of Ovidrel in bacteria and mammalian cell lines, chromosome aberration assay in human lymphocytes and in vivo mouse micronucleus have shown no indication of genetic defects.

Reviewer signature/team leader signature: /S/ 4/12/00

cc: HFD-580 file/Davis-Bruno/Jordan/Deguia /S/
Draft date: 4/12/00 Draft 3

Deguia

APR 12 2000

Review and Evaluation of Pharmacology/Toxicology Data

HFD-580/Karen Davis-Bruno; Ph.D.

NDA 21-149

Serono Laboratories

Submission: 11/26/99

Ovidrel (r-hCG; recombinant human choriogonadotropin)

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