I. GENERAL INFORMATION

A. File Number

NADA 139-237

B. Sponsor

Fort Dodge Laboratories
800 5th Street N.W.
Fort Dodge, Iowa 50501

C. Proprietary Name

Factrel®

D. Established Name

gonadorelin hydrochloride

E. Dosage Form

Sterile injectable solution

F. Dispensing Status

Prescription (Rx)

G. Dosage Regimen

100 µg/cow

H. Route of Administration

Intramuscular injection

I. Indication

Factrel® is indicated for the treatment of ovarian follicular cysts in cattle. The treatment effect of Factrel® when used in cattle with ovarian cysts is a reduction in the number of days to first estrus.

II. EFFECTIVENESS

Gonadorelin is the generic name adopted by the USAN Council for both naturally occurring and synthetic gonadotropin releasing hormone (GnRH). The gonadorelin base is a decapeptide with a molecular weight of 1182.33 and chemical formula of C55 H75 N17 O13. The amino acid sequence is identical to the natural hormone isolated from the hypothalamus of animals.

The New Animal Drug Application for Factrel® is based upon adequate and well controlled studies demonstrating clinical effectiveness and pertinent references from the scientific literature.

A. Dose Response Clinical Study, BA-83-3

Investigators:

Dr. R.L. Ax
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Madison, Wisconsin 53706

Dr. W.D. Wilson, Theriogenologist
River Valley Veterinary Clinic
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The purpose of the study was to determine the effects of various dosages of GnRH on the reproductive performance of cows with ovarian cysts.

Test animals included 85 mature cows, predominantly of the Holstein breed, in early lactation, with ovarian cysts, randomly assigned to one of four treatment groups:

Group	Treatment
1	Vechicle, control
2	50 µg Factrel®
3	100 µg Factrel®
4	250 µg Factrel®

Controls were given vehicle (without active drug) as a placebo.

Diagnosis of cystic ovaries was made by the attending veterinarian based on rectal palpation. Additionally, milk samples were taken at the time of treatment and again at seven and 14 days following treatment for progesterone determinations in an attempt to categorize the type of cyst. Those cows with milk progesterone <1 ng/mL were presumed to have follicular cysts while those with milk progesterone >1 ng/mL were presumed to have luteal cysts or partially luteinized follicular cysts.

Dosage form, dosage and route:

An injectable solution containing 50 µg GnRH per mL, identical to the product to be marketed, was used and given as a single intramuscular injection at a dose of 1, 2 or 5 mL per injection, corresponding to the dosages in the above table.

Duration:

The reproductive performance of the cows was monitored through subsequent estrus cycles and breeding(s) until pregnancy was confirmed or for a minimum of 60 days post treatment.

Pertinent parameters measured included the following primary parameters:

- Days to first estrus following treatment
- Days to conception after treatment
- Pregnancy rate by 60 days post treatment (%)
- % of cows conceiving at first estrus after treatment
- % of cows conceiving on second and third estrus

Results of dose response clinical study:

Pregnancy rate by 60 days post treatment (80%) and the highest first post treatment estrus conception rate (60%). There were no apparent differences between treatment groups with regard to average days to conception after treatment.

	Dose of GnRH (µg)			
Variable	**0**	**50**	**100**	**250**
No. of cows	22	22	20	21
Days to First Estrus After Treatment (mean ± sem)	46.1 ± 7.2	43.1 ± 5.9	40.3 ± 5.7	33.7 ± 4.7
Days to Conception After Treatment (mean ± sem)	45.1 ± 6.9	50.0 ± 6.6	48.2 ± 10.7	46.5 ± 7.1
Pregnancy Rate by 60 days Post-Treatment	63.6%	72/7%	80%	61.9%
No. Cows Conceiving on First Estrus	8(36%)	9(41%)	12(60%)	6(29%)
No. Cows Conceiving on Second and Third Estrus	6(27%)	7(32%)	4(20%)	7(33%)
Progesterone <1ng/mL at treatment (No. cows)	12	7	14	9
Progesterone >1ng/mL at Treatment (No. cows)	7	10	4	9
Days to First Estrus in Cows with progesterone <1ng/mL at Treatment (mean ± sem)	48.7 ± 9.6	31.0 ± 6.8	35.4 ± 6.6	39.4 ± 7.7
Days to First Estrus in Cows with progesterone >1ng/mL at Treatment (mean ± sem)	48.1 ± 15.9	43.0 ± 8.3	52.0 ± 14.4	28.6 ± 7.0

Based on milk progesterone levels, 42% of the cows had some degree of luteinization of the cyst at the time of treatment. Cows with milk progesterone <1 ng/mL (follicular cysts) appeared to respond well to GnRH, even at doses as low as 50 µg while cows with progesterone >1 ng/mL (luteinized cysts) appeared to respond better to the 250 µg dose.

No adverse reactions of any kind were reported in this study.

Conclusions drawn from dose response clinical study:

Results of this study suggest that (1) GnRH administration in cystic cows reduces time to first estrus, (2) 100 µg is a justifiable dose and (3) cows with follicular cysts respond better to lower doses than do cows with luteinized cysts.

B. Dose Confirmation Clinical Study BA-86-11

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The purpose of this clinical study was to compare the reproductive performance of cows with cystic ovaries treated with 100 µg GnRH with those given 250 µg GnRH.

Test animals included 207 mature cows predominantly of the Holstein breed, in early lactation with ovarian cysts, randomly assigned by a computer generated pre-assignment list to either the 100 µg or 250 µg dosage group.

Diagnosis of cystic ovaries was made by the veterinarian based on rectal palpation.

Dosage form, dosage, and route of administration:

An injectable solution containing 50 µg GnRH per mL, identical to the product to be marketed, was used and given as a single intramuscular injection at a dose of 2 or 5 mL per injection, corresponding to the respective dosages.

Duration:
The reproductive performance of the cows was monitored through subsequent estrus cycles and breeding(s) until pregnancy was confirmed or for a minimum of 60 days post treatment.

Pertinent parameters measured included the following primary parameters:

- Days to first estrus following treatment
- Days to conception after treatment
- % of cows conceiving at first estrus after treatment
- Cycle length following first estrus

Results of dose confirmation clinical study BA-86-11:

Complete follow up results were obtained in 172 of the cows as summarized in the following table. Data from remaining 35 cows were excluded because of failure to meet the criteria of the study protocol.

Parameter	**Dose (µg)**	**No. cows**	**Result**
Days, calving to treatment (mean)	100	89	54.4
Days, calving to treatment (mean)	250	101	63.5
Days, treatment to 1st estrus (mean)	100	81	22.8
Days, treatment to 1st estrus (mean)	250	91	23.7
Days from treatment to conception	100	56	36.8
Days from treatment to conception	250	58	32.0
Conception rate, 1st estrus breeding	100	36/59	61.0%
Conception rate, 1st estrus breeding	250	38/99	57.6%
Estrus cycle length following first estrus (mean,days)	100	35	28.4
Estrus cycle length following first estrus (mean,days)	250	37	22.6

The reproductive performance of cows given the 100 µg dose and cows given the 250 µg dose were similar.

No adverse reactions of any kind were reported in this study.

Conclusions drawn from the study:

Results of this study indicated that there was no discernible difference in response between the 100 and 250 µg GnRH doses, thereby further supporting the conclusion that 100 µg is a suitable dosage of GnRH in cows with cystic ovaries.

C. Comparative Clinical Studies BA-83-3, BH-84-7, BM-84-8 and BA-84-4

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The purpose of this clinical study was to compare the reproductive performance of cows with cystic ovaries treated with 100 µg GnRH as Factrel® with those given 100 µg GnRH as Cystorelin, an approved reference control product.

Test animals included a total of 355 mature cows predominantly of the Holstein breed, in early lactation with ovarian cysts, randomly assigned by a computer generated pre-assignment list to either the Factrel® or reference control dosage group. Eighty five of these test animals were excluded from data analysis because of failure to meet the criteria of the study protocol.

Diagnoses of cystic ovaries were made by the veterinarian based on rectal palpation.

Dosage form, dosage, and route:

An injectable solution containing 50 µg GnRH per mL, identical to the product to be marketed, or the reference control GnRH product were used and given as a single intramuscular injection at a dose of 2 mL per injection, corresponding to the 100 µg dosage.

Duration:

The reproductive performance of the cows was monitored through subsequent estrus cycles and breeding(s) until pregnancy was confirmed or for a minimum of 60 days post treatment.

Pertinent parameters measured included the following:

- Days to first estrus following treatment
- Days to conception after treatment
- % of cows conceiving at first estrus after treatment
- Pregnancy rate by 60 days post treatment (%)

Results of comparative clinical efficacy studies:

The results of this study were similar to the results of previous studies and were similar between the Factrel® and the reference control GnRH groups tested under identical conditions, as summarized in the following table:

GnRH CLINICAL RESULTS TABLE

Variable	**Factrel® (100µg)**	**Control GnRH (100µg)**
No. of Trials (Practices)	7	7
No. of Cows	149	121
Days to First Estrus After Treatment	32.4 ± 1.9	31.4 ± 2.3
Days to Conception After Treatment	44.0 ± 3.2	36.6 ± 3.4
No. Pregnant by 60 days Post Treatment (%)	103 (69.1%)	84 (69.4%)
No. Cows Conceiving on First Estrus	66 (44.3%)	48 (39.7%)
No. Cows Conceiving on Second and Third Estrus	36	36
Total Conceiving on Estrus 1-3	102 (68.4%)	84 (69.4%)

No adverse reactions of any kind were reported in these studies.

Conclusions drawn from comparative effectiveness clinical studies:

The results of these studies demonstrated that the clinical effectiveness of Factrel® is equivalent to that of the approved reference control GnRH when field tested under identical conditions and doses.

III. TARGET ANIMAL SAFETY

A. Subacute Safety Study in Target Animals, BA-85-9

Investigators:

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Wisconsin State Department of
Agriculture and USDA
Madison, Wisconsin

The purpose of the study was to determine whether or not overdosage of GnRH would be toxic to cows.

Test animals included eight normally cycling adult dairy cows; 4 Holsteins, 2 Ayrshires, a Jersey and a Guernsey; weighing between 980 and 1620 pounds, divided into treatment group of 4 cows and a control group of 4 cows.

Dosage form used was an injectable solution containing 50 µg GnRH per mL, identical to the product to be marketed. Controls were given diluent only, not containing GnRH.

Dosage, route and duration:

Treatment cows were given 2,500 µg GnRH (50 mL Factrel®) by deep intramuscular injection daily for 3 consecutive days while controls received 50 mL diluent according to the same route and schedule. This dosage regimen corresponds to 25X the recommended dose of GnRH for 3X the recommended duration.

Pertinent parameters measured included physical examination for general health and signs of injection site irritation daily, hematology, serum chemistry and urinalysis (except when no sample could be collected) determinations twice before treatment and 1, 2, 4 and 8 days after treatment began; determination of blood and milk progesterone activity before and after treatment; and necropsy and gross pathologic examination of 2 cows of each treatment group 5 days after the final injection.

Histopathology was performed on tissues from all organ systems and included pituitary, ovary, and uterus as well as any other tissues with apparent gross lesions.

Additionally, LH assays were performed on blood samples drawn from each of the four treatment cows and four control cows before and 0.5, 1, 2, 4 and 8 hours after the first and third intramuscular treatment.

Results of subacute toxicity study:

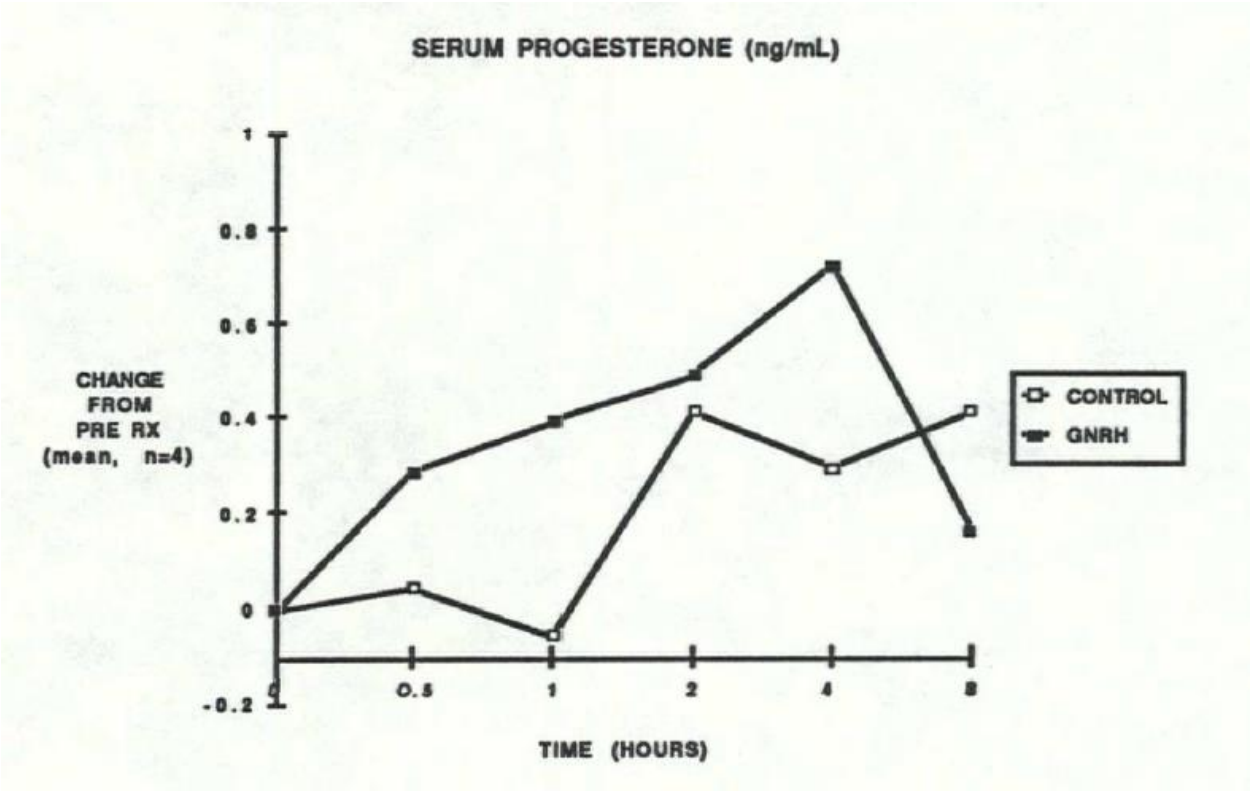
Physical examination daily revealed no signs of adverse effects in either group and no signs of injection site irritation. All cows maintained body weight and except for

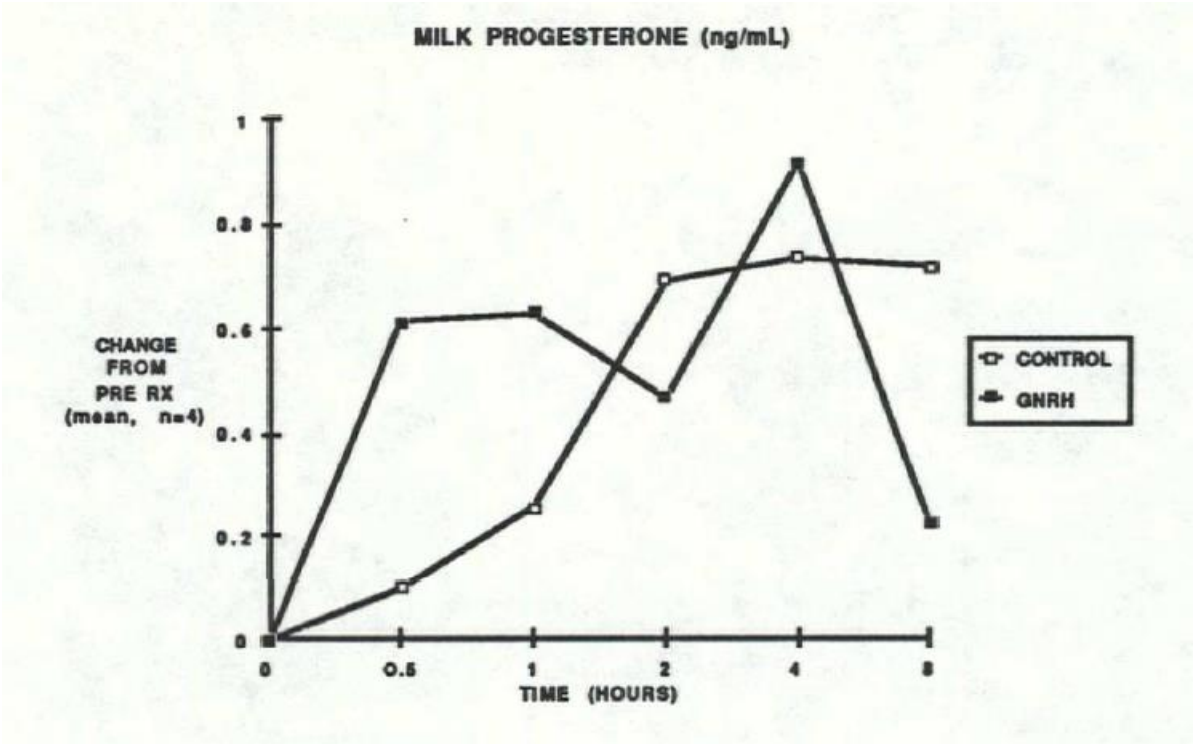
one cow of the control group, also maintained normal milk production throughout the study period.

Hematology and urinalysis results remained within normal limits throughout the study period. The only abnormalities noted on serum chemistry results were elevated creatinine phosphokinase (CPK) activity in 2 cows, 1 from each treatment group. This finding is attributable to muscle damage due to the intramuscular injection of large amounts of material (50 mL, three injections) and was no more prevalent in GnRH treated cows than in controls.

After the first injection of GnRH (but not placebo), serum LH concentrations increased as expected. After the third injection, however, almost no LH surge was detected, LH levels remaining close to basal levels. These LH results are summarized in more detail under "Human Food Safety".

No drug related effects on serum and milk progesterone determinations were detected as illustrated in the following charts:





At necropsy, no gross pathologic signs of injection site irritation were noted. No significant gross post mortem lesions were observed in the circulatory, respiratory, digestive, urinary, non-reproductive endocrine or central nervous systems. No gross lesions of reproductive organs were observed; ovaries were in various stages of follicular activity.

Histopathologic examination of pituitaries (the target tissue of GnRH) of all cows were within normal limits. Histopathology on reproductive organs of GnRH treated cows revealed changes expected following administration of GnRH in cycling cows: intense mitotic activity in germinal epithelium of ovary, congestion of endometrium and myometrium in the uterus.

Conclusions drawn from subacute toxicity study:

GnRH given at 25X overdosage daily over a 3X time period was without toxic effects in dairy cows as evidenced by physical examination, hematology, serum chemistry, urinalysis and gross and histopathologic examination.

B. Effect of 5X and 10X GnRH Dosage on Reproductive Performance

Investigator: This study is cited from the published literature (Dobson, H., Rankin, J.E.F. and Ward, W.R., Bovine Cystic Ovarian Disease: Plasma Hormone Concentration and Treatment Veterinary Record, 101:459, 1977)

The purpose of the study was to determine the hormonal status of cows with cystic ovaries and to evaluate treatment, including GnRH.

Test animals included 78 dairy cows with cystic ovaries of which ten with "low progesterone cysts" (follicular cysts) and 20 with " high progesterone cysts" (luteal cysts) were treated with GnRH.

The diagnosis of cystic ovaries were based on rectal palpation and determination of plasma progesterone and other reproductive hormone levels.

Dosage, route and duration were a single intramuscular injection of either 500 or 1,000 µg GnRH, corresponding to 5X and 10X the recommended dose of Factrel®.

Pertinent parameters measured included determination of cyst removal by rectal palpation seven days after treatment, number of cows showing estrus within 21 days, pregnancy rate, days to conception and average services per conception.

These parameters determined in GnRH treated cows were compared with those in human chorionic gonadotropin (HCG), progesterone and prostaglandin treated cows.

The results of the study are summarized in the table below. In the group with non luteinized follicular cysts, GnRH removed the cysts in 9 of 10 cows and resulted in less time and fewer services to conception than the "foreign" protein HCG with which it was compared. In the group with luteal cysts, GnRH treatment removed the cysts in 13 of 20 cows. Pregnancy rates were similar among treatments, indicating that GnRH given at these high dosages had no detrimental effect on reproductive performance.

Services	**Treatment**	**No.**	**Number responded (cyst removed)**	**Number in heat in <21 days**	**Number not pregnant**	**Days to conception mean ± SD**	**Per conception mean ± SD**
Low Progesterone Cysts	GnRH	10	9	4	5	13.6 ± 15	1.4 ± 0.8
Low Progesterone Cysts	HCG	11	8	5	3	31.8 ± 28	2.25 ± 0.96
High Progesterone Cysts	GnRH	20	13	7	10	37.1 ± 33	1.8 ± 1.1
High Progesterone Cysts	Progesterone	9	8	6	5	24.0 ± 7.5	1.5 ± 0.5
High Progesterone Cysts	Prostaglandin	28	27	26	16*	26.9 ± 27	1.91 ± 0.95

*This value includes four cows for which no information was available after service.
The results of this published study support the conclusion that GnRH given at 5X and 10X the recommended dosage has no adverse affect on fertility.

C. Safety Study of GnRH in sexually mature, cycling, non-pregnant cattle

Investigator:

Dr. B.R. Downey, DVM
McDonald College
St. Anne de Bellevue
Quebec, Canada

The purpose of the study was to determine the effect of GnRH on the length of the estrus cycle and any other adverse effects.

Test animals were four health heifers known to have had at least two estrus periods and had therefore completed at least one estrus cycle, divided into two treatment groups of two heifers each. Two heifers were treated on day 5, early luteal phase, of the estrus cycle and two heifers were treated on day 14, late luteal phase, of the estrus cycle.

Dosage form, route, dosage and duration were 500 µg GnRH in 4 mL Bacteriostatic Water for Injection, U.S.P., given as a single intramuscular dosage of 500 µg , the effects of which were followed throughout the subsequent estrus cycle (three to four weeks). The 500 µg dosage represents 5X the recommended clinical dose.

Pertinent parameters measured included pulse and respiratory rates 15 and 60 minutes post injection, observations for any apparent behavioral changes, palpation of the injection sites for any signs of local irritation, rectal palpation 14 days after treatment, and daily observation for any clinical abnormalities until estrus was observed.

Results of safety study in non-pregnant animals:

GnRH treatment under the conditions described had no clinical or behavioral effects in the heifers, nor did GnRH have any apparent effect on the length of the estrus cycle or condition of the uterus and ovaries, as summarized in the following table:

Parameter	**Day 5 Group**	**Day 5 Group**	**Day 14 Group**	**Day 14 Group**
Heifer No.	422	418	421	419
Pulse Rate – pretreatment	68	68	78	64
Pulse Rate – 15 min. post treatment	68	72	74	66
Pulse Rate – 60 min. post treatment	84	70	68	66
Respiration Rate – pretreatment	22	20	24	26
Respiration Rate – 15 min. post treatment	24	20	26	24
Respiration Rate – 60 min. post treatment	24	22	24	24
Behavior – pretreatment	normal	normal	normal	normal
Behavior – 15 min. post treatment	normal	normal	normal	normal
Behavior – 60 min. post treatment	normal	normal	normal	normal
Estrous cycle (days) – pretreatment	25	32	23	26*
Estrous cycle (days) – post treatment	24	30	21	21
Uterine and ovarian cond. – pretreatment	normal	normal	normal	normal
Uterine and ovarian cond. – post treatment	normal	normal	normal	normal

*Mean length of two previous cycles.

Conclusions drawn from safety study in nonpregnant heifers:

The findings in this study were consistent with those in the published literature (Seguin, Oxender, and Britt, Am. J. Vet. Res., 38:1153, 1977) in which it was reported that administration of 100 µg GnRH during the mid-luteal phase did not affect corpus luteum function or the duration of the estrus cycle.

It was therefore concluded that administration of GnRH to nonpregnant heifers presents no hazard of toxicity.

D. Safety Study of GnRH in first, second or third month of gestation

Investigator:

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The purpose of the study was to determine the effects of GnRH on early pregnancy, and any other adverse effects.

Test animals were nine healthy, pregnant Holstein or Ayrshire cows divided into three groups. Extra cows were included in the 30 day treatment group since pregnancy could not be confirmed by rectal palpation. Treatment groups were therefore as follows:

- 30 day treatment: 5 cows (4 pregnant, 1 non pregnant)
- 60 day treatment: 2 cows, pregnant
- 90 day treatment: 2 cows, pregnant

Dosage form, route, dosage and duration were 500 µg GnRH in 4 mL Bacteriostatic Water for Injection, U.S.P., given as a single intramuscular dosage of 500 µg , the effects of which were followed throughout the subsequent four to six weeks. The 500 µg dosage represents 5X the recommended clinical dose.

Pertinent Parameters Measured included observation for any clinical abnormalities and confirmation of pregnancy by rectal palpation.

Results:

Of the four cows treated at 60 or 90 days of pregnancy (diagnosed pregnant by rectal palpation prior to treatment), all were confirmed pregnant by rectal palpation four to six weeks after GnRH treatment. Of the five cows treated 30 days after breeding (and therefore presumed to be pregnant), four were confirmed pregnant by rectal palpation four to six weeks after GnRH treatment. The return to estrus by one cow 13 days after treatment was not considered drug related since this estrus occurred almost exactly two cycle lengths following breeding, indicating that she had not conceived.

Conclusions drawn from the safety study in pregnant cows:

The results of this study using a 5X overdosage lead to the conclusion that the administration of GnRH to sexually mature, pregnant cows presents no hazard of toxicity.

E. Effect on Fertility in Cows with Ovarian Cysts, BA-86-11 (summarized previously in "Effectiveness")

Investigator:

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Dept. of Dairy Science
Univ. of Wisconsin
Madison, Wisconsin 53706

Data from this Dose-Response Confirmation field study were utilized to asses the effects of 100 µg dosage vs. 250 µg dosage on reproductive performance of cattle with cystic ovaries. As part of the data generation, the effect of each dosage of Factrel® on interval to first estrus and conception rate to first service was recorded. No difference was noted between these two dosage levels.

Parameter	**GnRH Dose Group 100 µg**	**GnRH Dose Group 250 µg**
No. of cows	81	91
Interval to 1st estrus after Factrel® treatment	22.8 days	23.7 days
Conception Rate to breeding at 1st estrus (%)	36-59 (61%)	38/66 (57.6%)

Conclusions based on results of this study were that a 2.5X overdosage of Factrel® was not detrimental to reproductive function in the cow.

IV. HUMAN FOOD SAFETY

GnRH is a naturally occurring peptide in cattle as well as humans and, like many endocrine hormones, is rapidly broken down into inactive metabolites, having a half life of 4 minutes in humans (Arimura et al, 1974. Clin. Endocrinol. 3:421; Redding et al, J. Clin. Endocrinol Metab. 1973. 37:626) and 7 minutes in the rat (Redding & Schally. 1973. Life Sciences. 12:23). The action of GnRH is to stimulate the pituitary to release gonadotropins, chiefly luteinizing hormone (LH) which in turn acts on the ovary causing ovulation, subsequent luteinization of the follicle, and release of progesterone. The most sensitive assay for exogenously administered GnRH is, therefore, the detection of increased levels of LH in the blood.

Since it is a naturally occurring peptide, it is not surprising that background levels of GnRH, reportedly ranging from 0.5 to 3 ng/mL have been found in normal milk from untreated cows (Baran & Koch, 1976, Science, 198:300).

The active ingredient in Factrel® is identical in structure to the naturally occurring peptide. In order assure the safety to consumers of milk and meat from treated cows, studies were focused on determining whether use of this particular GnRH product as proposed (1) results in GnRH levels in serum milk that exceed normal background and (2) results in LH levels or subsequent progesterone levels that exceed those expected from normally cycling cows.

A. GnRH Disappearance from Blood and Milk in the Cow (Trial BN-86-10)

Investigator:

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Test Substances:

Factrel® (gonadorelin hydrochloride) 50 µg /mL, identical to that to be marketed. Placebo (vehicle for Factrel® without GnRH. Positive control (approved reference control product, Cystorelin, 50 µg /mL)

Test Animals included 20 non pregnant, lactating dairy cows at the stage of lactation when ovarian cysts are common, randomly divided into five groups of four cows each and given a single intramuscular injection as follows:

Placebo control	4 cows	0X (2mL)
Factrel®, 100 µg	4 cows	1X (2mL)
Factrel®, 250 µg	4 cows	2.5X (5mL)
Factrel®, 1,000 µg	4 cows	10X (20mL, 4 injection sites of 5mL)
Postive control GnRH	4 cows	1X (2mL)

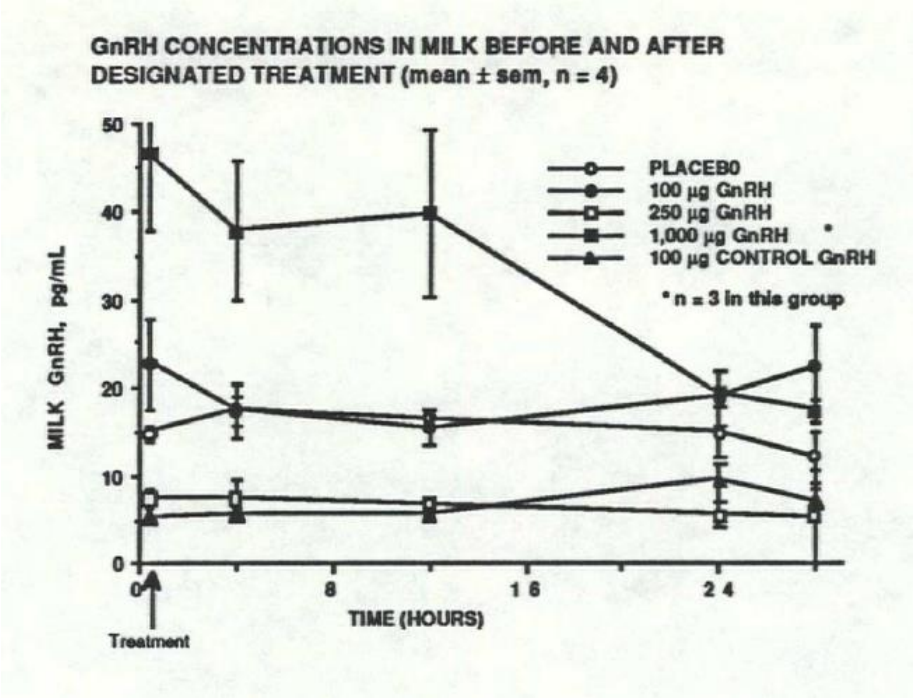
Blood samples were collected before treatment and at 5, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes and 12 hours after injection. Milk samples were collected before treatment and 4, 12, 24 and 28 hours after treatment.

GnRH and LH activity were determined on blood samples and GnRH activity in milk samples, both by radioimmunoassay. The sensitivity of the GnRH radioimmunoassay method, defined conservatively as the quantity of GnRH that reduces binding of 125-I-GnRH to 90% of B-0 (binding value when no GnRH is added) was 0.6 pg/mL, corresponding to less than 1 part per trillion. Additionally, SGOT was determined in blood serum collected before and 12 hours after treatment to determine whether evidence of muscle damage would be found.

Results of serum GnRH determinations showed that concentrations of GnRH are detectable within five minutes after intramuscular injection, reach their maximum level within 15 minutes and generally return to preinjection baseline levels by 90 minutes as summarized in the following table:

Time (minutes)	Serum GnRH, pg/mL (mean ± sem, n = 4)				
	Placebo	100 µg GnRH	250 µg GnRH	1,000 µg GnRH	100 µg Control
0	ND	0.8 ± 0.2	0.5	ND	0.9
5	0.3	3.6 ± 1.3	8.7 ± 1.9	9.9 ± 2.6	4.9 ± 2.0
15	0.4	6.0 ± 1.0	9.7 ± 1.2	14.8 ± 4.1	4.9 ± 1.2
30	ND	2.5 ± 1.2	7.4 ± 1.0	9.5 ± 2.3	5.0 ± 1.5
60	ND	1.4 ± 0.7	1.9 ± 0.8	0.9	3.6 ± 1.8
90	ND	0.6	0.7	1.0	0.9 ± 0.3
120	ND	0.8	ND	1.2	ND
150	1.6	ND	ND	0.9	ND
180	ND	1.6	ND	ND	0.4
210	ND	0.3	ND	ND	ND
240	ND	ND	ND	ND	ND
270	ND	0.7	ND	ND	ND
300	0.6	ND	ND	ND	ND
12 HR	ND	1.5	ND	ND	ND

Results of milk GnRH determinations showed a significant level of GnRH immunoreactivity in milk of all cows prior to administration of GnRH. The background level of GnRH did not increase following treatment with either product at any dosage tested. One cow of the 1,000 µg group had a milk GnRH concentration of 330 pg/mL before treatment (which declined rapidly at samplings subsequent to treatment). The milk GnRH data (above cow excluded) are summarized in the following chart illustrating that GnRH injection at doses up to 1,000 µg (ten times the recommended dose) did not increase GnRH in milk.



Results of LH determinations in plasma showed an increase in LH following each of the doses of GnRH given. The LH response to GnRH was extremely variable, most

likely due to the particular stage of the estrus cycle that each cow happened to be in at the time of treatment. The LH results are summarized in the following table:

Time (minutes)	**Serum LH, ng/mL (mean ± sem, n = 4)**				
	Placebo	**100 µg GnRH**	**250 µg GnRH**	**1,000 µg GnRH**	**100 µg Control**
0	0.3 ± 0.1	0.4	0.3	0.1	0.6
5		7.9 ± 5.6	1.5 ± 0.5	4.4 ± 0.9	3.4 ± 0.6
15	1.0	8.3 ± 4.1	4.1 ± 2.0	1.9 ± 0.7	9.5 ± 6.2
30	0.2	4.0 ± 1.3	10.3 ± 2.5	2.3 ± 0.5	11.5 ± 4.3
60	0.2 ± 0.1	2.7 ± 0.7	5.9 ± 2.5	14.2 ± 6.6	13.1 ± 2.9
90	0.1	2.1 ± 0.6	13.2 ± 7.5	21.7 ± 14.0	42.1 ± 29.4
120	0.3 ± 0.2	1.6 ± 0.5	19.4 ± 7.0	19.3 ± 8.4	40.4 ± 16.9
150	0.2	1.9 ± 1.2	19.2 ± 7.9	8.4 ± 2.3	45.1 ± 15.6
180	0.5	1.6 ± 0.8	8.5 ± 3.4	6.3 ± 1.3	22.8 ± 6.9
210	0.2 ± 0.1	0.5 ± 0.2	4.1 ± 0.7	2.2 ± 0.9	13.7 ± 7.4
240	0.3	0.6 ± 0.2	2.7 ± 1.3	3.7 ± 1.1	3.8 ± 1.3
270	0.8	0.5 ± 0.2	1.9 ± 0.6	1.1 ± 0.6	2.0 ± 0.8
300	0.2	0.3	0.9 ± 0.3	0.8 ± 0.3	1.5 ± 0.7
12 HR	0.2	0.5	0.1	0.3	0.2

Results of SGOT determinations showed no evidence of muscle damage in that SGOT remained within normal limits in all cows at all doses following treatment.

No side effects or other evidence of toxicity of any kind was encountered in the study.

Conclusions drawn from the study:

Intramuscular injection of GnRH as Factrel® at dosages of 100, 250 or 1,000 µg/cow (1X, 2.5X and 10X the recommended dose) results in blood plasma GnRH concentrations that exceed background concentrations for only about 90 minutes in cows. GnRH treatment does not result in milk GnRH concentrations that exceed background levels after 24 hours of treatment, even at 10X the recommended dose. These results are similar to those demonstrated with the approved reference control GnRH product given at its recommended dose of 100 µg /cow.

Intramuscular injection of GnRH at all doses tested also results in moderate increases in LH activity in serum as expected, and these LH levels are similar to those reported during the preovulatory surge in normal cows (7-55 ng/mL, Echternkamp & Hansel, 1973, J An Sci, 37:1362).

It can therefore be concluded that use of GnRH as recommended does not pose any health hazard to human consumers of milk or meat from treated cows.

B. Effect of GnRH at 1X and 10X Dose on LH and Progesterone in Cows (BA-85-9)

Investigator:

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The purpose of this study was to determine the effects of exogenous GnRH on luteinizing hormone (LH) levels, and, additionally, progesterone, in cows. Since GnRH levels in serum and milk following exogenous GnRH are very low and transient, LH was chosen as the most sensitive endpoint possible.

Test substance was Factrel® (gonadorelin hydrochloride) 50 µg/mL, identical to that to be marketed. Control substance was the vehicle only, not containing GnRH.

Test animals included 12 non pregnant, lactating dairy cows at the stage of lactation when ovarian cysts are common, divided into three groups and given a single intramuscular injection as follows:

Placebo control	3 cows	0X (2mL)
Factrel®, 100 µg	5 cows	1X (2mL)
Factrel®, 1,000 µg	4 cows	10X (20mL, 2 injection sites)

Blood samples were collected before treatment and at 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes and 12, 24, 36 and 48 hours after injection. Milk samples were taken before treatment and 12, 24, 36 and 48 hours after treatment. LH and progesterone assays were determined on blood and milk samples by radioimmunoassay methods. The sensitivity for LH was 43 +/- 9 pg/mL for LH.

Results of blood serum LH determinations showed that, under conditions of this study, intramuscular GnRH dosage of 100 µg elicited only slight release of LH but these concentrations were not different from those in control cows. Administration of 1,000 µg GnRH resulted in an increase in serum LH which peaked at 1.5 hours at an average of 27.74 ng/mL.

Time (hrs.)	Serum LH (ng/mL, mean ± sem)		
	0 µg(3)	**100 µg (5)**	**1,000 µg(4)**
-24	0.03 ± 0.05	0.28 ± 0.27	0.07 ± 0.04
0.0	0.00 ± 0.00	0.09 ± 0.10	0.17 ± 0.23
0.5	0.10 ± 0.14	1.60 ± 1.01	4.20 ± 1.55
1.0	0.36 ± 0.43	1.37 ± 0.81	22.19 ± 10.28
1.5	0.11 ± 0.10	1.85 ± 1.24	27.74 ± 14.41
2.0	0.09 ± 0.01	2.02 ± 1.64	21.71 ± 11.31
2.5	0.40 ± 0.40	1.28 ± 1.30	9.18 ± 3.29
3.0	0.17 ± 0.07	0.99 ± 0.82	9.70 ± 4.90
3.5	0.10 ± 0.02	0.43 ± 0.57	3.93 ± 1.68
4.0	2.42 ± 2.46	0.36 ± 0.39	2.67 ± 1.26
4.5	1.19 ± 1.22	0.38 ± 0.27	1.69 ± 0.63
5.0	0.15 ± 0.04	0.18 ± 0.06	1.38 ± 0.77
24	0.67 ± 0.50	0.52 ± 0.49	0.15 ± 0.03

Results of serum and milk progesterone determinations revealed no changes or differences among doses of 0, 100 or 1,000 µg GnRH. The average pretreatment serum levels of progesterone varied from 2.12 ng/mL, 3.39 ng/mL and 4.96 ng/mL depending on the group of test animals. Post treatment determinations of progesterone showed no indication of change over the 24 hours test period.

The average pretreatment level of progesterone in milk varied from 2.72 ng/mL, 4.32 ng/mL and 5.41 ng/mL depending on the group of test animals. No dose response elevation of milk progesterone was noted in cows post treatment as compared to the control group.

Sample	Time (hrs.)	PROGESTERONE (ng/mL, mean ± sem)		
		0 µg(3)	**100 µg(5)**	**1,000 µg(4)**
Serum	-24	2.08 ± 1.45	3.37 ± 2.09	5.10 ± 1.37
Serum	0.0	2.17 ± 0.64	3.41 ± 1.36	4.82 ± 0.66
Serum	0.5	1.95 ± 0.41	3.94 ± 1.16	6.45 ± 0.55
Serum	1.0	2.12 ± 0.80	3.49 ± 0.87	5.79 ± 0.45
Serum	1.5	1.98 ± 0.06	3.51 ± 0.58	5.14 ± 0.23
Serum	2.0	1.82 ± 0.17	3.14 ± 0.39	5.17 ± 0.45
Serum	2.5	1.78 ± 0.31	3.40 ± 0.39	5.72 ± 1.30
Serum	3.0	2.36 ± 0.69	3.13 ± 0.26	5.23 ± 1.07
Serum	3.5	2.04 ± 0.77	3.17 ± 0.68	5.49 ± 1.07
Serum	4.0	1.88 ± 0.67	3.04 ± 0.54	5.67 ± 1.61
Serum	4.5	1.92 ± 0.37	2.91 ± 0.42	5.09 ± 1.42
Serum	5.0	1.99 ± 0.56	3.18 ± 0.93	5.75 ± 1.81
Serum	24	1.87 ± 0.48	2.45 ± 0.86	2.04 ± 2.43
Milk	-24	2.67 ± 2.99	3.55 ± 1.29	4.41 ± 1.24
Milk	0	2.77 ± 0.92	5.09 ± 1.29	6.41 ± 1.76
Milk	12	6.85 ± 5.20	9.12 ± 3.95	3.66 ± 1.76
Milk	24	5.34 ± 2.13	8.55 ± 3.81	4.46 ± 2.45
Milk	36	0.87	-	2.36 ± 0.23
Milk	48	0.35	-	-

Conclusions drawn from the study:

Exogenous GnRH injection had only a transient effect on LH concentrations and no effect on serum or milk progesterone concentrations. (Blood progesterone levels range from 0.0 ng/mL to 4.8 +/- .49 ng/mL depending on stage of estrus cycle, Echternkamp & Hansel, 1973, J An Sci, 37:1362.) (Progesterone in whole milk ranges from 0 to 20 ng/mL depending on stage of estrus cycle, Pope, Majklik, Ball and Leaver, 1976, Brit Vet J, 132:497.)

Inasmuch as LH and progesterone levels remained within the range expected in normally cycling cows, it can be concluded that use of GnRH as recommended does not pose any health hazard to human consumers of milk or meat from treated cows.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of 512 of the Act and demonstrate that Factrel® when used under its proposed conditions of use, is safe and effective for the labeled indications.

The agency has granted an exemption under 21 CFR 201.105 from the requirement of "adequate directions for use" in section 502(f)(1) of the Act. Therefore, labeling will restrict this drug to use by or on the order of a licensed veterinarian. This decision was based on the requirement that a differential diagnosis and monitoring of patient progress requires the professional expertise of a veterinarian.

VI. ATTACHMENTS

Factrel® package label
Factrel® package insert

Copies of these labels may be obtained by writing to the:

Food and Drug Administration

Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.