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# FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-339

OVUGEL

Triptorelin Acetate  
Gel  
Swine, Weaned Sows

For synchronization of time of insemination in weaned sows to facilitate a single fixed-time artificial insemination.

Sponsored by:

JBS United Animal Health II LLC

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I. GENERAL INFORMATION:

- A. File Number: NADA 141-339
- B. Sponsor: JBS United Animal Health II LLC  
322 S. Main St.  
Sheridan, IN 46069  
  
Drug Labeler Code: 051233
- C. Proprietary Name(s): OVUGEL
- D. Established Name(s): Triptorelin acetate
- E. Pharmacological Category: Protein Hormone
- F. Dosage Form(s): Gel
- G. Amount of Active Ingredient(s): 100 mcg triptorelin per mL (as triptorelin acetate)
- H. How Supplied: 52.5 mL multi-dose bottle
- I. How Dispensed: OTC
- J. Dosage(s): Single 2 mL dose (200 mcg triptorelin per dose)
- K. Route(s) of Administration: Intravaginal
- L. Species/Class(es): Swine, Weaned sows
- M. Indication(s): For the synchronization of time of insemination in weaned sows to facilitate a single fixed-time artificial insemination.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

1. Title: Dose Justification Study for Triptorelin Gel Treatment: Time of Ovulation Following Intravaginal Triptorelin Gel in Post Partum Sows; Study No. PTK-003
2. Study Locations: The Swine Research Center at the University of Illinois in Urbana, IL and the United Feeds Research Farm (UFRF) in Sheridan, IN.
3. Study Design
  - a) Objective: The primary objective of this study was to optimize the dose of triptorelin acetate included in a 1.2% methylcellulose gel, administered intravaginally 96 hours after weaning, to effectively synchronize time of ovulation in postpartum sows.
  - b) Study Animals: Following a 13 to 30 day lactation at each farm, 130 sows were randomly assigned to one of four treatments: 1) Control (0 mcg triptorelin), 2) TG-25 (25 mcg triptorelin), 3) TG-100 (100 mcg triptorelin), or 4) TG-200 (200 mcg triptorelin). Thirty-two (treatments 1 and 2) or 33 (treatments 3 and 4) sows were allotted to each treatment group. All sows were weaned and maintained in environmentally regulated facilities with boars housed in separate rooms, and/or a minimum of 40 feet away and downwind.
  - c) Test Article Administration: Sows were treated by intravaginally administering the test article (2 mL of vehicle gel for control animals or 2 mL of vehicle gel containing 25, 100, or 200 mcg triptorelin for treated animals) approximately 0.5 inches posterior to the cervix with a modified insemination catheter. A new catheter was used for each pig. The test article was administered to each animal in the morning on the day that 30 to 40% of the sows were expected to be in estrus (96 hours post-weaning for sows at both farms; Table 1). According to standard commercial practice, sows were inseminated daily while they were in estrus.

The formulation of triptorelin gel in this study contained 25, 100, or 200 mcg of triptorelin (supplied as the acetate salt) in 1.2% methylcellulose in phosphate buffered saline. The vehicle gel contained 1.2% methylcellulose in phosphate buffered saline.

Table 1. Percent of animals expressing estrus on the morning of treatment.

Study Site	Sows, n	Treatment time, hours post-weaning	% sows in estrus
Swine Research Center	31	96	32.3 %
UFRF <sup>1</sup>	100	96	52.0 %

<sup>1</sup> One sow was removed following treatment because she had ovulated prior to treatment, therefore the treatment could not have a possible effect on the sow

4. Measurement and Observations: All sows were observed once for estrus on the day before treatment (Day -1), and three times daily for three consecutive days beginning on the day of treatment (Day 0 - Day 3), or until the sow no longer showed signs of estrus.
5. Statistical Methods: Effectiveness was determined by the percentage of sows ovulating within 40 to 48 hours post-treatment. Sow parity, lactation length, and average size of the largest follicles on Day 4 post-weaning were included as covariates. The 5 percent level of significance ( $P \leq 0.05$ ) was used for all hypothesis tests (two-tailed).
6. Results: Treatment had no effect on the percentage of sows ovulating by 24, 32, or 40 hours following treatment ( $P > 0.05$ ), however, by 48 hours a greater percentage ( $P = 0.0051$ ) of sows treated with 200 mcg triptorelin (81%) had ovulated compared to the controls (42%). The percentage of sows dosed with 25 or 100 mcg of triptorelin (63% and 64%, respectively) did not differ from either the control or the 200 mcg dose.
7. Conclusions: This study supports the target dose of 200 mcg triptorelin per 2 mL dose volume in a 1.2% methylcellulose gel and dosing regime of 1 dose administered intravaginally at 96 hours post-weaning in sows to be inseminated.

B. Substantial Evidence:

1. Title: Effectiveness of Triptorelin Gel to Synchronize the Time of Insemination in Postpartum Sows; Study No. PTK 9-06
2. Study Investigators and Locations:
  - a) William Flowers, Ph.D.; J.C. Howard Farms, Deep Run, NC
  - b) Paul Yeske, D.V.M. and Laura Schulz, D.V.M.; Wakefield Pork Inc., Bingham Lake, MN
  - c) Michael Johnston, M.S.; T.C. Bache Farm, Frankfort, IN
  - d) Rafael Kummer, D.V.M. and Marcelo Almeida; The Maschhoffs Inc., Carlyle, IL
  - e) Raymond Schmitt, Ph.D.; Seaboard Foods, Guymon, OK
3. Study Design:
  - a) Objective: The primary objective of this study was to demonstrate the effectiveness of OVUGEL (200 mcg triptorelin per 2 mL dose), administered intravaginally to sows approximately 96 hours after weaning, to synchronize insemination in order to facilitate a single fixed-time insemination approximately 20 hours after treatment.
  - b) Study Animals: A total of 1,886 healthy postpartum sows (parity 1 to 7; Table 2) were used across the five study sites. Sows were weaned

following a three-week lactation. Study animals were chosen from breeding herds representative of major swine producing regions in the United States.

Table 2. Breed of sows used at each of the five study sites.

Study Site	Breed of Sows
J. C. Howard Farms	Newsham hybrid
Wakefield Pork Inc.	PIC Line C-22
T. C. Bache Farm	PIC Line C-22 PIC Line C-29
Maschhoffs Inc.	PIC maternal line
Seaboard Foods	Large white x Landrace

- c) Treatment Groups: Sows at each site were blocked for parity and lactation length, and randomly assigned to one of two treatment groups (100 sows per treatment; Table 3). An additional 200 non-treated sows per site were included in the study as contemporary sows and were monitored for four weeks prior to and four weeks after administration of the test article in study sows. Contemporary sows were used to compare study sows with animals inseminated daily for multiple days based upon the sow's estrous behavior, per standard industry practice.

Table 3. Test article and insemination practice for each treatment.

Treatment	Test Article	Insemination
Formulation A	Intravaginal vehicle gel (0 mcg triptorelin)	Single fixed time (20 h post-treatment)
Formulation B	Intravaginal triptorelin gel (200 mcg triptorelin)	Single fixed time (20 h post-treatment)

- d) Test Article Administration: Sows were treated by intravaginally administering the test article (2 mL of vehicle gel for control animals or 2 mL of vehicle gel containing 200 mcg triptorelin for treated animals) approximately 0.5 inches posterior to the cervix. The test articles were administered to each animal approximately  $96 \pm 4$  hours after weaning.

Doses were delivered with a commercially available applicator. A new disposable sheath surrounded the catheter and was replaced for each sow. The formulation of OVUGEL used in this study contained 200 mcg of triptorelin (supplied as the acetate salt) in 1.2% methylcellulose based formulation. The vehicle gel contained the same ingredients as OVUGEL, with the exception of containing no triptorelin.

4. Measurement and Observations: Approximately  $22 \pm 2$  hours after treatment, all treated sows were inseminated once. A boar was present in front of the sows at time of insemination.

Sows were observed for signs of estrus, which was used as an indicator of non-pregnancy, for 18 to 24 days following insemination. To elicit signs of estrus, a mature boar was walked in front of the sows, exposing each animal to visual, auditory, and olfactory signals from the boar for up to five

minutes. Estrus was confirmed when a sow responded to back pressure by standing rigidly, flexing the ear, and ceasing vocalization. Other measurements included daily general health observations, adverse event observations, and detection of pregnancy via trans-abdominal ultrasonography between 23 and 36 days post-insemination.

Conception rate [(No. of females pregnant divided by the No. of females in the group that were bred) times 100] was determined and used to define effectiveness. Pregnancy rate [(No. of females pregnant divided by the No. of females in the group) times 100], farrowing rate [(No. of females delivering offspring divided by the No. of females in the group) times 100], and piglet index [(total No. of live piglets born divided by the No. of females in the group) times 100] were collected and also supported product effectiveness. Pregnancy failure, gestation length, date of farrowing, number of live piglets born, live litter birth weight, number of stillborn and mummified piglets, and pre-weaning piglet mortality per litter were recorded. On day of weaning, the date, number of pigs weaned and litter weaning weight were recorded.

5. Statistical Analysis: The primary response variable was conception rate. Pregnancy rate, conception rate and farrowing rate were analyzed by the GLIMMIX procedure in SAS, with treatment, parity, lactation length, and the associated 2-way interactions included as fixed effects. Site, block (site) and site by treatment interaction were included as random effects, assuming a binomial distribution. The piglet index was analyzed by the GLIMMIX procedure in SAS, assuming a Poisson distribution.

Except where noted, safety variables were analyzed by the GLIMMIX procedure in SAS, with treatment, parity, pre-treatment lactation length, and the associated 2-way interactions included as fixed effects. Pregnancy failure rate was analyzed without random affects and assuming binomial distribution. Gestation length was analyzed without random effect and assuming Poisson distribution. Number of stillborn piglets was analyzed with site and the site by treatment as random affects, assuming a Poisson distribution. Mummified piglet numbers were analyzed with block (site), site and the site by treatment as random affects, assuming a Poisson distribution. Live and total piglets per litter were analyzed with site as a random effect, assuming a Poisson distribution. Live litter birth weight, adjusted litter birth weight, and litter weaning weight were analyzed by the MIXED procedure in SAS with block (site), site, and site by treatment as random effects and assuming a normal distribution. Median days from weaning to estrus were analyzed using the LIFETEST procedure, where the resulting P-values are the approximate probability values of the partial chi-square statistics for the Log-rank test.

## 6. Results:

- a) Effectiveness variable – Conception rate: A total of 485 animals receiving the vehicle gel and 490 animals receiving OVUGEL were evaluated for conception rate (Table 4). Conception rate was significantly higher ( $P = 0.0195$ ) for the OVUGEL treated group than for the vehicle treated group. The treatment by pre-treatment lactation

length interaction was also significantly different ( $P = 0.0272$ ) and the estimated slope of pre-treatment lactation length for the vehicle treated group was higher than for the OVUGEL group, suggesting that the administration of OVUGEL reduces the effect of pre-treatment lactation length on conception rate.

Table 4. Conception rate of sows treated with the vehicle gel or OVUGEL.

	Vehicle Gel	Triptorelin Gel
Conception Rate, % <sup>1</sup>	80.04	85.63
Treatment P-value	0.0195	0.0195
Parity P-value	0.4936	0.4936
Lactation Length P-value	0.0363	0.0363
Treatment x Parity P-value	0.8739	0.8739
Treatment x Lactation Length P-value	0.0272	0.0272
Parity x Lactation Length P-value	0.6069	0.6069

<sup>1</sup> Percent values represent the back-transformed values derived from the statistical model. Counts are the raw counts of 5 study sites.

- b) Other variables: Results for pregnancy rate are exactly the same as those for conception rate (80.04% for vehicle gel; 85.63% for OVUGEL), since all sows in the OVUGEL and vehicle treated groups were bred.

Farrowing rate was significantly higher ( $P = 0.0167$ ) for OVUGEL treated sows than for vehicle treated sows (84.16% vs. 77.11%, respectively). There was also a significant interaction between treatment and the sow's previous lactation length ( $P = 0.0234$ ) and the estimated slope of farrowing rate for the control group was significantly higher than for the OVUGEL group, suggesting that the administration of OVUGEL reduces the effect of pre-treatment lactation length on farrowing rate.

The piglet index was significantly greater ( $P = 0.0048$ ) for OVUGEL treated sows than for vehicle treated sows, with a difference of 137 piglets between the two treatment groups (896 vs. 759 piglets, respectively). This equates to a 1.37 live piglet per sow increase due to the use of OVUGEL when sows are inseminated only once approximately  $22 \pm 2$  hours after treatment.

Reproductive and piglet safety variables: There were no significant treatment effects ( $P > 0.10$ ) between the OVUGEL and vehicle treated groups for the following measured variables: pregnancy failure rate, gestation length, number of stillborn piglets per litter, number of mummified piglets per litter, actual and adjusted live litter birth weight, number of live piglets per litter, pre-weaning piglet mortality per litter, litter weaning weight, days from weaning to estrus, total piglets per litter, and piglets weaned per litter.

7. Conclusions: Administration of OVUGEL significantly increased the conception rate of sows artificially inseminated once approximately  $22 \pm 2$  hours after treatment. Administration of OVUGEL also improved farrowing rate and the number of live piglets produced, and is considered safe when administered intravaginally to weaned sows at the labeled dose and



according to labeled directions. The data support the effectiveness of OVUGEL for the synchronization of time of insemination in weaned sows to facilitate a single fixed-time artificial insemination.

### III. TARGET ANIMAL SAFETY:

#### A. Margin of Safety Study

1. Title: "Swine Safety Study in Postpartum Sows", Stillmeadow Inc., Study No. 10272-06.
2. Study Investigators and Location: Vicki S. Crutchfield and Janice O. Kuhn, Ph.D.; T.C. Bache Farm, Frankfort, IN
3. Study Design:
  - a) Objective: The objective of this study was to evaluate the safety of a single 1X (200 mcg) and 7X (1400 mcg) dose of triptorelin gel following intravaginal application to postpartum sows 96 hours following weaning.
  - b) Study Animals: Twenty-four lactating postpartum sows were selected based on health history records and clinical examinations. Within three days post-weaning, the sows were divided into three cohorts based on parity, body weight, and weaning date. Equal numbers from each cohort were randomly assigned to one of three treatments: a control group, sows dosed with 2 mL (200 mcg) triptorelin gel (1X), or sows dosed with 14 mL (1400 mcg) triptorelin gel (7X).
  - c) Test Article Administration: Intravaginal gel containing 100 mcg/mL triptorelin acetate (triptorelin gel) was used as the test article and intravaginal gel with 0 mcg/mL triptorelin acetate (vehicle) was used as the control. Each dose of test or control article was drawn into the appropriate sized syringe (6 mL for 2 mL dose; 20 mL for 14 mL dose) and administered intravaginally at the proximal end of the vagina near the cervix. Each sow in the control group was administered 2 mL of the control article approximately 96 hours after weaning. Each sow in the 1X group received 2 mL of the test article and sows in the 7X group received 14 mL of the test article at approximately 96 hours after weaning.
4. Measurements and Observations: In-life phase monitoring included twice daily clinical evaluations from weaning through to necropsy, observation and measurement of body weight, feed consumption, and evidence of vaginal irritation or infection (discharge). Whole blood and serum were analyzed for general hematology, serum chemistry, and serum endocrine function parameters. Urine was collected prior to necropsy and evaluated for specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, and microscopic examination of the sediment. Necropsy occurred two days post-dosing. At necropsy, gross observations were made for all external surfaces, orifices, and internal organs found in the cranial, thoracic and abdominal cavities. The following organs were weighed and gross lesions were described: adrenal glands, brain, left and right kidneys, heart, left

and right ovaries, reproductive tract, pituitary gland, and parathyroid. Sections of the following tissues were collected for preservation: endocrine system (pituitary, thyroid, thymus, parathyroid, adrenal, pancreas, and ovaries), entire reproductive tract, mammary gland, cerebrum, heart, liver, spleen, bone marrow, kidney, duodenum, jejunum, mesenteric lymph node, lung, urinary bladder, and any abnormal tissue.

5. Statistical Methods: Continuous response variables were analyzed using mixed effects analysis of covariance with pre-study body weight as a covariate. Repeated measures analysis of covariance with a baseline measure of the variable as a covariate was used for the in-life continuous responses measured at multiple time points. Cohort was not considered in the statistical analysis.
6. Results:
  - a) *In-Life Observations:* Weight loss, due to the normal rapid regression of mammary tissue following the end of lactation, was noted between weaning and day of necropsy for all sows. Mean weight loss did not differ among the three treatment groups (Table 5). Feed consumption remained consistent throughout the study.

Table 5. Live performance results.

Treatment	Mean Body Weight Loss, lbs	Mean Daily Feed Consumption, lbs/day
Vehicle Gel	20.6	5.00
Triptorelin Gel, 1X	19.4	4.98
Triptorelin Gel, 7X	23.5	4.98

*Clinical observations:* Inflammatory lesions and abscesses on the ears, head, neck, shoulder, abdomen, and/or tail were noted during pre- and post-dose observations, but were mild in nature and were considered to be benign, as these are common occurrences in swine in a commercial production system. All other observations (healing lesions, an ear hematoma, and small lumps on the neck or shoulder), were graded as normal, non-dose related occurrences. Incidence of vaginal discharge was noted in two sows of the control group post-dosing, but not in either group administered the test article.

*Clinical pathology:* With the exception of elevated globulin and creatine phosphokinase (CPK) levels, serum chemistry results were within 0 to 2% of the reference range for all treatment groups and were not considered to be abnormal. Mean CPK (Table 6) and globulin (Table 7) levels were both higher than reference range for all groups and were not dose-dependent. Overall, there were only minor abnormal findings in the hematology results and any deviations from the reference range were not considered to be dose-dependent. Urinalysis results were within the reference range for all treatment groups. Mean luteinizing hormone (LH) values were elevated in treated sows in comparison to control animals (Table 8), which is consistent with triptorelin's mechanism of action.

Table 6. Mean CPK values<sup>1</sup>, measured in U/L.

Treatment	Day 0, Baseline <sup>2</sup>	Day 0, 2 h	Day 0, 5 h	Day 2
Vehicle Gel	1206	508	557	757
Triptorelin Gel, 1X	411	614	558	1646
Triptorelin Gel, 7X	789	1481	648	653

<sup>1</sup> Reference range for CPK: 230-416 U/L<sup>2</sup> Baseline is prior to dosing on Day 0; h: approximate hour after dosingTable 7. Mean globulin values<sup>1</sup>, measured in g/dL.

Treatment	Day 0, Baseline <sup>2</sup>	Day 0, 2 h	Day 0, 5 h	Day 2
Vehicle Gel	3.7	3.7	3.6	3.7
Triptorelin Gel, 1X	3.8	3.8	3.7	3.9
Triptorelin Gel, 7X	4.0	4.1	3.9	4.0

<sup>1</sup> Reference range for globulin: 2.6-3.5 g/dL<sup>2</sup> Baseline is prior to dosing on Day 0; h: approximate hour after dosing

Table 8. Mean luteinizing hormone values, measured in ng/mL.

Treatment	Day 0, Baseline <sup>1</sup>	Day 0, 2 h	Day 0, 5 h	Day 2
Vehicle Gel	1.4	1.9	1.9	1.4
Triptorelin Gel, 1X	1.9	2.1	2.8	1.5
Triptorelin Gel, 7X	1.8	3.1	2.9	1.9

<sup>1</sup> Baseline is prior to dosing on Day 0; h: approximate hour after dosing

## b) Postmortem Observations:

*Gross necropsy:* Necropsy findings included a yellow-white material in the urine of one animal from the control group and an abscess on the right ham (rear quarter) of one animal from the 7X dose group.

*Microscopic pathology:* Sows from all three treatment groups displayed cysts on the thyroid gland, pituitary gland, lymph node, kidneys, and/or ovaries. These were considered to be incidental, mild in nature, and commonly seen in swine raised in a swine production facility.

A single animal in the 1X group presented with cerebral laminar necrosis. This was determined to be non-dose related.

Inflammation of the vaginal tissues was found in two sows of the control group, four sows of the 1X dose group and 3 sows of the 7X dose group. The inflammation was considered to be minor and did not adversely affect the sows.

*Organ weights:* With the exception of the kidneys, absolute organ weights were not affected by treatment. Absolute kidney weight was greater in animals of the 7X dose group (666.70 g) in comparison to control animals (571.68 g). Relative kidney weights did not differ

between treatment groups and no compound related pathological findings were noted.

7. Conclusions: Triptorelin gel is safe when administered to weaned sows at the labeled dose. Intravaginal administration of triptorelin gel to post partum sows at approximately 96 hours after weaning may cause minor vaginal inflammation that is non-dose related. An approximate 4.5% decrease in weight was associated with the regression of mammary tissue following weaning. No dose-related abnormalities were detected for serum chemistry, hematology, urinalysis, or serum endocrine function results.

#### IV. HUMAN FOOD SAFETY:

##### A. Microbial Food Safety (Antimicrobial Resistance)

The use of OVUGEL (triptorelin) to synchronize the time of insemination and facilitate a single fixed-time insemination in weaned sows (swine) is not thought and has not been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated animals. The Agency determined that an assessment of the microbial food safety (antimicrobial resistance) associated with this use of OVUGEL (triptorelin) in post-weaning sows (swine) was not necessary at this time.

##### B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of OVUGEL (triptorelin) in or on the edible tissues of treated weaned sows (swine) are not thought and have not been reported to impact the intestinal flora of human consumers. The Agency determined that an assessment of the impact of residues or metabolites of OVUGEL (triptorelin) in the edible tissues of treated weaned sows (swine) on human intestinal flora was not necessary at this time.

##### C. Toxicology Hazard Identification and Characterization

Triptorelin belongs to a class of drugs called gonadotropin releasing hormone agonists (GnRHa) and is a synthetic deca-peptide agonist analog of natural GnRH. Peptides are degraded by intestinal enzymes and are generally poorly bioavailable when given orally. Identification and characterization of the hazard associated with chronic and acute oral exposures to triptorelin were achieved using data obtained from a 45-day oral toxicity study that included a measurement of acute effects and by evaluating all other available information related to triptorelin and GnRH analogs.

The hypothesis of the 45-day oral toxicity study was that oral triptorelin acetate, administered at a dose calculated to be the theoretically highest possible dose to which humans could be exposed through consumption of edible tissues of OVUGEL treated sows, would have no biological or toxicological effects on male or female rats, as measured by luteinizing hormone (LH), selected steroids, clinical pathology and histopathology. The rationale for assessing LH levels in this study was that a single injection of triptorelin induces a measurable LH spike 1 to 4 hours post-treatment and, therefore, the absence of an LH spike following oral administration of triptorelin acetate would provide

evidence of its lack of oral bioavailability. Because down regulation of the LH release from the pituitary occurs following chronic injections of triptorelin, a lack of down regulation of LH release following chronic oral administration would further confirm the absence of triptorelin acetate oral bioavailability.

The 45-day subchronic toxicology study is summarized below:

1. Title of the Study: 45-day safety study of orally or subcutaneously administered triptorelin acetate to male and female rats, Study No. 1695-002
2. Report Date: December 16, 2011
3. Study Director and Location (in life): Joyce Heward, M.S., DABT; MPI Research, Inc., Mattawan, MI.
4. Purpose: The purpose of this GLP study was to evaluate the safety of the test article, triptorelin acetate, when administered via oral gavage (PO) or via subcutaneous (SC) injection once daily for 45 consecutive days or as a single oral dose to male and female rats, and to determine if triptorelin acetate, given orally to rats, has any biological or toxicological effects at a maximum human potential exposure dose with an additional 31X safety factor.
5. Experimental Design: Naïve CD (CrI:CD(SD)) rats (10 per sex per group) received triptorelin acetate via oral (PO) gavage at doses of 0.25, 1, and 4 mcg/kg of bodyweight (bw) per day, or via subcutaneous (SC) injection at doses of 4 and 400 mcg/kg bw per day for 45 consecutive days. On Day 14, all PO animals or SC animals dosed with 4 mcg/kg bw per day received a subcutaneous dose of 400 mcg/kg bw triptorelin acetate. The control animals received the vehicle (0.5% methylcellulose in distilled water) via oral gavage and were given 400 mcg/kg bw subcutaneous injection on Day 14. General observations, clinical observations and ophthalmoscopic examinations were performed. Body weight and food consumption were recorded. Vaginal smears were collected via lavage from all female animals throughout the study for estrous stage determination. Blood samples for LH evaluation were collected from all males on Day 1 and from all animals at Days 14 and 46 (necropsy). Blood samples for testosterone analysis were collected from all male animals pretest and at necropsy. Blood samples for estradiol and progesterone analyses were collected from all females observed in diestrus on one occasion during the pretest period and during last week of dosing. Blood and urine samples for standard clinical pathology evaluations (clinical chemistry, hematology, and urinalysis) were collected from all animals prior to the scheduled terminal necropsy. At study termination, necropsy examinations were performed, a standard set of organ weights (per VICH GL#31) and weights of additional organs and tissues (lung with bronchi, salivary gland, seminal vesicles with coagulating gland, pituitary and thyroid gland with parathyroid) were recorded, and a complete set of tissues were collected and examined microscopically.

In addition, satellite groups of female rats (10/group) received the vehicle or test article formulation in the same manner as the main groups at doses

of 0 (PO), 4 (PO), 4(SC), and 400 (SC) mcg/kg bw once on Day 1. The estrous cycle was monitored from all female rats by daily vaginal smears, starting the day after arrival and throughout the study. Blood samples for LH evaluation were collected from all female animals on Day 1, after which the animals were euthanized and the carcasses were discarded.

6. Results: There were no biologically or toxicologically significant treatment-related effects on any of the endpoints measured in rats given triptorelin orally. These endpoints included clinical and ophthalmoscopic observations, body weight, food consumption, clinical pathology, estrous cycle, hormones, and pathology. In contrast, subcutaneous administration of triptorelin at 4 or 400 mcg/kg bw/day revealed multiple findings, including (1) increases in body weights in females at both doses; (2) cessation of estrous cycling by 32 and 17 days of dosing at 4 and 400 mcg/kg bw/day, respectively; (3) dose-response increases in serum LH concentrations of females and males at both doses on Day 1; (4) marked decreases in serum testosterone concentrations in males at both doses, and decreases in serum progesterone in females at both doses were also noted; (5) macroscopic findings (smaller uteri with cervixes testes and seminal vesicles with coagulating glands at both doses, smaller ovaries and enlarged adrenal glands at 400 mcg/kg bw/day); (6) changes in organ weights with corresponding microscopic findings (increased adrenal gland weights in females at 400 mcg/kg bw/day, decreased uteri with cervixes weights at 4 and 400 mcg/kg bw/day, and decreased weight of seminal vesicle with coagulating gland and testes at 400 mcg/kg bw/day; and (7) microscopic findings in the ovaries and uteri with cervixes of females at both doses, vaginas at 400 mcg/kg bw/day, testes, epididymides, prostate glands and seminal vesicles with coagulating glands at 400 mcg/kg bw/day, adrenal glands of females at 400 mcg/kg bw/day, and in the bone marrow and mammary glands of males and females at 400 mcg/kg bw/day. Following subcutaneous injection of triptorelin on Day 14, all animals in the control and orally dosed groups had an increase in serum LH concentrations, while the serum LH concentration did not increase in the subcutaneously dosed animals; these results indicated that the LH receptors of the control and orally dosed animals had not been desensitized by continuous exposure of triptorelin, while the subcutaneously dosed animals showed LH receptor desensitization.
7. Conclusion: It was concluded that there was a lack of biologically or toxicologically significant effects in male and female rats following 45 consecutive days of daily treatments or a single oral administration of triptorelin acetate up to the highest dose tested (4 mcg/kg bw/day).

The 45-day rat study, together with other available information related to triptorelin or GnRH analogs and their use in human medicine as well as other information in the literature, provides sufficient evidence that triptorelin, like other members of its class of GnRH analogs, will have very low oral bioavailability in humans consuming edible tissues from OVUGEL-treated sows.

#### D. Assessment of Human Exposure to Triptorelin Residues

Traditional residue chemistry studies were not conducted for this approval. The Agency considered traditional residue chemistry studies inappropriate for the determination of triptorelin residue concentrations or metabolic profiles in sows because triptorelin is a small peptide that is susceptible to proteolysis in vivo. The Agency evaluated a worst-case residue exposure assessment conducted by the sponsor where the worst-case residue concentrations in the edible tissues of sows treated with OVUGEL were calculated and used to calculate the worst-case potential human exposure to triptorelin residues due to consumption of the edible tissues.

The worst-case exposure assessment over-estimates the amount of triptorelin residues that might be present in the individual edible tissues because drug absorption, distribution, metabolism, and elimination will take place after the administration. This will result in a reduction of the drug residues in the edible tissues to less than those predicted by the worst-case assessment.

By using a worst-case assessment, the Agency ensures that the human food safety decisions made in the absence of information obtained through traditional residue chemistry studies are protective of the public health.

#### A Worst-Case Assessment for Potential Human Exposure to Triptorelin Residues

The assessment assumes that an average sow weighs 214 kg, and the muscle, liver, kidney, and fat of sows make up 54.5, 1.3, 0.6, and 35.0%, respectively, of the body weight. The worst-case assessment also assumes that: 1) the entire intravaginal dose of triptorelin is absorbed by sows; 2) none of the dose is eliminated from the sows or degraded during the 12 hours between the administration of the product and slaughter of the sows; and 3) the entire 200 mcg triptorelin dose is distributed to each of the four edible tissues (muscle, liver, kidney or fat). The results of the worst-case assessment of potential human exposure to triptorelin residues in muscle, liver, kidney and fat are summarized in Table 9.

Table 9. A worst-case assessment of potential human exposure to triptorelin residues in edible tissues of sows receiving 200 mcg of triptorelin.

Edible Tissue	Tissue Weight Percentage of Live Weight of Sows, %	Tissue Weight Based on 214 kg Sows, kg	Total Tissue Residue Concentration from 200 mcg Triptorelin, mcg/g	Human Exposure to Residues, mcg/person/day	Human Exposure to Residues, mcg/kg bw/day
Muscle	54.5	116.6	0.0017	0.51	0.009
Liver	1.3	2.8	0.0714	7.14	0.119
Kidney	0.6	1.3	0.1538	7.69	0.128
Fat	35.0	74.9	0.0027	0.14	0.002

Example calculations from Table 9:

Column 3, Kidney:  $214 \text{ kg} \times 0.6\% = 1.3 \text{ kg kidney}$

Column 4, Kidney:  $200 \text{ mcg triptorelin}/1300 \text{ g kidney} = 0.1538 \text{ mcg/g}$

Column 5, Kidney:  $0.1538 \text{ mcg/g} \times 50 \text{ g (food factor)}$   
 $= 7.69 \text{ mcg triptorelin/person/day}$

Column 6, Kidney:  $7.69 \text{ mcg triptorelin}/60 \text{ kg bw}$   
 $= 0.128 \text{ mcg triptorelin/kg bw/day}$

#### E. Human Food Safety Assessment

The calculated worst-case maximum human exposure to triptorelin residues due to consumption of the edible tissues of weaned sows (swine) treated with OVUGEL (0.128 mcg/kg bw/day) is 31-fold lower than the highest dose tested in the 45-day toxicology study in rats that demonstrated no effects (4 mcg/kg bw/day).

$$4 \text{ mcg/kg bw/day} \div 0.128 \text{ mcg/kg bw/day} = 31$$

We conclude that the 31-fold ratio between the minimum no-effect value obtained from the rat study and calculated maximum human exposure provides a sufficient margin to ensure the safety of human consumers. This conclusion is based on the following considerations related to exposure duration and interspecies differences: (1) The 45-day subchronic study was appropriately designed to address effects due to chronic exposure, and a longer duration of exposure would not be expected to increase the severity of any effects; (2) non-human mammalian GnRH is similar to human GnRH (the peptide is conserved across species, and is not species-specific) and the mechanism of action (receptor-mediated) is similar across species. Therefore, we conclude that the use of OVUGEL in weaned sows (swine) does not cause human food safety concerns at zero withdrawal.

#### F. Human Food Safety Parameters

1. Target Tissue and Marker Residue: It is not necessary to assign a target tissue or a marker residue for triptorelin residues in weaned sows (swine).
2. Tolerance: It is not necessary to assign a tolerance for triptorelin in edible tissues of weaned sows (swine).
3. Withdrawal Period: No withdrawal period is required (i.e., a zero withdrawal) for the use of OVUGEL in weaned sows (swine).

#### G. Analytical Method for Residues

A regulatory analytical method for monitoring triptorelin residues in edible tissues of weaned sows (swine) is not required.

#### V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to OVUGEL:



WARNINGS:

WITHDRAWAL PERIOD:

No withdrawal period is required when used according to labeling.

USER SAFETY WARNINGS:

Not for Use in Humans. Keep Out of Reach of Children. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

ANIMAL SAFETY WARNINGS:

OvuGel™ should not be used in sows with obvious reproductive tract abnormalities.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that OVUGEL, when used according to the label, is safe and effective for the synchronization of time of insemination in weaned sows to facilitate a single fixed-time artificial insemination. Additionally, data demonstrate that residues in food products derived from weaned sows treated with OVUGEL will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.