Date of Approval: March 27, 2020

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-322

Improvest®

gonadotropin releasing factor analog-diphtheria toxoid conjugate

Injectable Solution

Gilts intended for slaughter

For the temporary suppression of estrus in gilts intended for slaughter

Sponsored by:

Zoetis Inc.

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# I. GENERAL INFORMATION

## A. File Number

NADA 141-322

## B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

## C. Proprietary Name

Improvest®

## D. Drug Product Established Name

Gonadotropin releasing factor analog-diphtheria toxoid conjugate

## E. Pharmacological Category

Immunotherapeutic

## F. Dosage Form

Injectable solution

## G. Amount of Active Ingredient

0.2 mg gonadotropin releasing factor analog-diphtheria toxoid conjugate (GnRF analog-DT conjugate) per mL

## H. How Supplied

250 mL vial

## I. Dispensing Status

Rx

## J. Dosage Regimen

Two, 2-mL (0.4 mg gonadotropin releasing factor analog-diphtheria toxoid conjugate) injections. The first dose should be administered no earlier than 9 weeks of age. The second dose should be administered at least 4 weeks after the first dose. In case of incomplete dosing, the animal should be re-dosed immediately.

## K. Route of Administration

Injection, subcutaneous

### L. Species/Class

Gilts intended for slaughter

### M. Indication

For the temporary suppression of estrus in gilts intended for slaughter.

### N. Effect of Supplement

This supplement provides for the addition of the indication for the temporary suppression of estrus in gilts intended for slaughter.

## II. EFFECTIVENESS

### A. Dosage Characterization

This supplemental approval does not change the previously approved two, 2-mL (0.4 mg GnRF analog-DT conjugate) injections administered no earlier than 9 weeks of age, and at least 4 weeks apart. The Freedom of Information (FOI) Summary for the original approval of NADA 141-322 dated March 22, 2011, and supplemental approval dated November 30, 2011, contains dosage characterization information for boars[1]. Additionally, two published literature references (McCauley et al., 2003[2]; Oliver et al., 2003[3]) in gilts and boars provide justification for using the same dosage regimen in both sexes.

### B. Substantial Evidence

Substantial evidence was evaluated by data to support the indication for the temporary suppression of estrus in gilts intended for slaughter. The endpoint evaluated in the clinical field study was estrus detection. Additionally, one supporting clinical field study evaluated the effect of the GnRF analog-DT conjugate (Improvac™) on estrus-related endpoints in gilts including: immune response, ovarian size, and ovarian maturity. The formulation of Improvac™ and Improvest® are identical. In this supplemental FOI Summary, CVM concludes that Improvest® is safe and effective for the temporary suppression of estrus in gilts intended for slaughter when used according to labeling.

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[1] The use of "boars" and "intact male pigs" have been used interchangeably herein, and on product labeling, and previous NADA 141-322 Freedom of Information Summaries.
[2] McCauley I, Watt M, Suster D, Kerton D, Oliver W, Harrell R, and Dunshea F. 2003; 54, 11-20. A GnRF vaccine (Improvac™) and porcine somatotropin (Reporcin) have synergistic effects upon growth performance in both boars and gilts. Australian Journal of Agricultural Research.
[3] Oliver W, McCauley I, Harrel R, Suster D, Kerton D, and Dunshea F. 2003; 81, 1959-1966. A gonadotropin-releasing factor vaccine (Improvac™) and porcine somatotropin have synergistic and additive effects on growth performance in group-housed boars and gilts. Journal of Animal Science.

1. Clinical Field Study

**Title:** Evaluation of the efficacy of Improvest® in suppressing estrus in gilts intended for slaughter (Study #C121C-US-17-019)

**Study Dates:** October 2018 to March 2019

**Study Location:** Dalhart, TX

**Study Design:**

Objective: The objective of this study was to evaluate the effectiveness of Improvest® for the temporary suppression of estrus in gilts intended for slaughter when administered at approximately 9 and 20 weeks of age and slaughtered at 30 weeks of age. This study was conducted following Good Clinical Practices (GCP).

Study Animals: A total of 40 prepubescent, Large White x Landrace crossbred gilts, approximately 9 weeks of age, were enrolled in this study.

Experimental Design:

*Treatment Groups:*

Table II.1. Treatment Groups

| Treatment Group | Treatment | Dose | Number of Animals |
|---|---|---|---|
| T01 | Sterile Saline Control | 2 mL | 20 |
| T02 | Improvest® | 2 mL (0.4 mg) | 20 |

*Randomization, Blocking, and Masking:* Gilts were randomized using a complete block design. The individual pig was the experimental unit. The Investigator and individuals who performed observations and/or recorded data were masked to treatment. The treatment administrator and the data recorder for treatment administrations were unmasked and not involved in other study observations or data recordings.

*Inclusion Criteria:* Gilts were required to be:

- Of the same genetic stock
- From a herd representative of the US swine industry
- Physically healthy upon enrollment in the study
- Born within a maximum of 14 days of each other
- Pre-pubescent

*Exclusion Criteria:* Gilts were ineligible for study enrollment if they:

- Were treated with an immunosuppressive or an immunostimulating drug prior to Day 0
- Were injected in the neck within 4 weeks prior to Day 0
- Had visible or palpable lumps in the neck area at Day 0
- Were unthrifty or lame

*Withdrawal Criteria:* Gilts were withdrawn from the study if:

- They were deemed by a veterinarian to be in poor or declining general health and either could not be treated without jeopardizing the study or did not respond to therapeutic treatment
- Any pig withdrawn was not replaced

Drug Administration: Gilts assigned to group T01 received a subcutaneous injection of sterile saline, and gilts assigned to group T02 were injected subcutaneously with Improvest®, in the post-auricular region of the right side of the neck on Day 0 (approximately 9 weeks of age). Gilts in both T01 and T02 were injected a second time subcutaneously with their respective treatment in the left side of the neck on Day 77 (approximately 20 weeks of age).

Measurements and Observations: From two weeks prior to the second treatment administration (Day 63) through the end of study (Day 147; slaughter), gilts were observed daily for detection of estrus using the back- pressure test (standing response) in the presence of a mature boar. General health observations and adverse event observations were monitored from Day 0 through Day 147.

**Statistical Methods:** A generalized linear mixed model was used to analyze a determination of "if estrus was ever detected" between the two weeks post- second injection and the end of the study. The distribution of this primary endpoint was considered binomial and the logit link was implemented in the generalized linear mixed model. Treatment was included as a fixed effect in the model and pen was included as a random effect. Back-transformed least squares means, 95% confidence intervals, and standard errors for treatment were calculated.

All hypothesis tests were conducted at the 0.05 level of significance (two- tailed).

**Results:** Effectiveness was evaluated in 38 gilts (19 gilts in the Improvest® group (T02) and 19 gilts in the saline control group (T01)). Two gilts, (1 gilt from T01 and 1 gilt from T02) were removed during the study according to withdrawal criteria. Improvest® was considered to be effective if there was a statistically significant difference between T01 and T02 gilts for estrus detection results. Estrus was evaluated for each gilt beginning two weeks post

second injection (Day 91) through the end of the study (Day 147). A positive estrus determination (standing heat) at any time from day 91 to 147 was recorded as estrus detected. The back-transformed least squares means percentage of gilts with estrus detected at least once from Day 91 through Day 147 was 4.5% (1 gilt with positive estrus detection) in the group treated with Improvest®, compared to 58.7% (11 gilts with a positive estrus detection) in the group treated with saline. A statistically significant difference (P = 0.0057) was observed between the group treated with Improvest® and the group treated with saline.

**Adverse Reactions:** All adverse reactions reported were followed daily until the animal recovered, was removed from study, died, or completed the study. The most common adverse reactions reported included lameness and rectal prolapse which are consistent with typical health observations seen in U.S. swine production facilities. No test article related adverse reactions were observed in this study.

**Conclusion:** Administration of Improvest® (two, 2-mL (0.4 mg) injections) is effective for the temporary suppression of estrus in gilts intended for slaughter.

2. Clinical Field Study

**Title:** The Effect of GnRF Conjugate on the Growth Performance and Carcass Traits of Finishing Gilts (Study #3322E-60-06-450)

**Study Dates:** October 2006 to December 2006

**Study Location:** Terre Haute, IN

**Study Design:**

Objective: The objective of this GCP study was to evaluate the effect of GnRF-DT conjugate immunization on the growth performance and carcass quality of finishing gilts.

Study Animals: A total of 280 Large White Landrace X Red Duroc crossbred gilts, approximately 18 weeks of age, were enrolled in this study. A total of 140 gilts (T01 and T02) were used in the evaluation of Effectiveness of Improvest®.

Experimental Design:

*Treatment Groups:*

Table II.2. Treatment Groups

| Treatment Group ID | Treatment Group | Dose/Dosage | Effectiveness Evaluation # of gilts |
|---|---|---|---|
| T01 | Sterile Saline Control | 2 mL | 70 |
| T02 | Improvac™ | 2 mL (0.4 mg) | 70 |

*Randomization and Blocking:* Gilts were randomized using a randomized complete block design. The experimental unit was the pen.

Drug Administration: Gilts in the T02 treatment group were injected subcutaneously in the neck with Improvac™ on Day 0 (approximately 18 weeks of age) and on Day 28 (approximately 22 weeks of age).

Measurements and Observations: Injection site reactions were assessed for Target Animal Safety (see Section III). Blood samples for anti-GnRF titers and hormone assays (progesterone and cortisol) were collected from gilts on Day 27, prior to administration of the second dose of Improvac™, and on Day 56, four weeks after administration of the second dose of Improvac™ and prior to slaughter. At necropsy (Day 56), ovaries were removed, combined, weighed, and scored in relation to the number and size of developing follicles and corpora lutea.

**Statistical Methods:** The anti-GnRF values were logarithmically transformed. The transformed anti-GnRF levels were analyzed using a general linear mixed model for repeated measures. The fixed effects in the model were treatment, time point and treatment by time point interaction. The random effects in the model were block, block by treatment interaction (pen term), animal within block and treatment, block by treatment by time point interaction, and residual. Treatment least squares means and 95% confidence limits were calculated for each time point as well as the minimums and maximums. A comparison between T01 and T02 was performed using contrasts.

Total ovary weight was analyzed using a general linear mixed model. The fixed effect in the model was treatment; random effects were block, block by treatment interaction and residual. Treatment least squares means, 95% confidence intervals and the minimums and maximums were calculated. A comparison between T01 and T02 was performed using contrasts.

All hypothesis tests were conducted at the 0.05 level of significance (two- tailed).

**Results:** A statistically significant difference ($P < 0.0001$) was observed between the group treated with Improvac™ (T02) and the group treated with saline (T01) for anti-GnRF titer and ovary weight.

Table II.3 Summary of Final Results

| **Variable** | **Study Day** | **Control T01** | **Improvac™ T02** | **P value T01 vs. T02** |
|---|---|---|---|---|
| Mean Ovarian Weight (g) | 56 | 7.85 | 3.83 | P < 0.0001 |
| Ovarian Evaluation: No Follicles (# gilts (%)) | 56 | 0 | 56 (80%) | N/A |
| Ovarian Evaluation: Immature Follicles (# gilts (%)) | 56 | 66 (94%) | 13 (18.6%) | N/A |
| Ovarian Evaluation: Mature Follicles (# gilts (%)) | 56 | 4 (5.7%) | 0 | N/A |
| Ovary Evaluation: Luteal Tissue (# gilts *%)) | 56 | 0 | 1 (1.4%) | N/A |
| Anti-GnRF titer (relative units) | 56 | 10.0 | 302.3 | P < 0.0001 |

**Adverse Reactions:** The most common adverse reactions reported were injection site reactions. Incidence, size, and persistence of injection site reactions were consistent with observations made in the previous boar studies (NADA 141-322 FOI Summary, dated March 22, 2011). See the Target Animal Safety section (Section III) for additional information. No other test article related adverse reactions were observed in this study.

**Conclusions:** Administration of Improvac™ significantly increased serum anti-GnRF antibody levels, reduced ovarian weight, and suppressed ovarian follicular maturation in gilts. Estrus-related endpoint results support and validate the effectiveness of Improvest® for the suppression of estrus in gilts intended for slaughter.

## III. TARGET ANIMAL SAFETY

CVM did not require target animal safety (TAS) studies for this supplemental approval. In addition to previously submitted TAS information for the original and supplemental approvals, CVM used the field study described above and additional information to support target animal safety. The GnRF analog-DT conjugate antigen in Improvest® generates an immune response that cross-reacts with and neutralizes endogenous GnRF, thereby inhibiting the hypothalamic-pituitary-gonadal axis. This mode of action is identical in male and female pigs. The FOI Summary for the

original approval of NADA 141-322 (dated March 22, 2011), contains a summary of TAS studies for intact male pigs intended for slaughter. Improvest® did not cause any direct pharmacological effects following administration in intact male pigs (e.g., GnRF activity, diphtheria toxin-like effects). In intact males, the major consequences of treatment were local and systemic inflammatory responses to injection, and atrophy of testes, prostate, and bulbourethral glands. The Good Laboratory Practices (GLP) TAS studies conducted for the original approval provide a complete description of the effects of Improvest® in pigs for all systems, except the reproductive system of gilts.

The TAS for the use of Improvest® in gilts intended for slaughter was determined by: 1) the use of reproductive system-related endpoints as indicators of general health, 2) a safety evaluation of the female reproductive system (e.g., uterine and ovary size and function) as part of the field effectiveness study (Study #3322E-60-06-450 above), and 3) the previously evaluated GLP safety studies in intact male pigs. Together these data demonstrate the safety of Improvest® for the indication and dosage regimen as described in Section I. General Information.

Furthermore, data from Study #9320C-08-11-362 (Evaluation of the Safety of Improvac™ in Suppressing Estrus and Estrus-related Behavior in Entire Iberian Female Pigs in Spain) was also used to evaluate adverse events including signs of systemic and local reactions following administration of Improvac™. Gilts (n=20 per treatment group) were treated with either saline (T01) or Improvac™ at approximately 18, 22, 34 weeks of age (T02) or 18, 22, 34, and 46 weeks of age (T03). Health observations, injection site reactions, and loss of edible tissues at slaughter from this study and Study #3322E-60-06-450 were consistent with observations evaluated during the TAS studies in intact males.

When administered to gilts, Improvest® did not cause unusual clinical signs or an unexpected frequency, severity, or persistence of injection site reactions. While there were no cases of anaphylactoid/anaphylactic reactions seen in gilts intended for slaughter in the U.S. clinical field studies, we note that these types of reactions have been reported in gilts outside of the U.S. Those anaphylactoid/anaphylactic reactions are consistent with those seen in intact male pigs intended for slaughter during post-approval field use both within and outside of the U.S. A description of anaphylactoid/anaphylactic – type reactions and their related clinical signs are included in the package insert of the approved U.S. product.

## IV. HUMAN FOOD SAFETY

### A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of GnRF analog-DT conjugate on microbial food safety (antimicrobial resistance) among bacteria of public health concern in or on treated swine. We considered that:

1) GnRF analog-DT conjugate is not regularly considered to have properties that would exert antimicrobial resistance pressure towards the emergence or selection of bacteria of public health concern,
2) GnRF analog-DT conjugate is not used to treat zoonotic gastroenteritis or other bacterial disease in humans,

3) GnRF analog-DT conjugate (or a similar compound) is not under development to treat bacterial diseases in humans, and
4) GnRF analog-DT conjugate is not indicated for a bacterial disease in a food- producing animal species.

Therefore, the Agency determined there was no need to develop or submit for review any microbial food safety (antimicrobial resistance) information or data regarding this use of GnRF analog-DT conjugate for the temporary suppression of estrus in gilts intended for slaughter.

## B. Toxicology

Reassessment of the acceptable daily intake (ADI) or acute reference dose (ARfD) was not needed for this supplemental approval. The ADI is 1.32 µg/kg bw/day derived from a 45-day subchronic oral toxicity study in rats. The ARfD is 6.6 µg/kg bw/day derived from an acute oral toxicity study in rats. The FOI Summary for the original approval of NADA 141-322, dated March 22, 2011, contains a summary of all toxicology studies and information.

## C. Safe Concentrations for Total Residues in Edible Tissues and Injection Sites

Reassessment of the safe concentrations for total residue of GnRF analog-DT conjugate were not needed for this supplemental approval. The safe concentrations for total residues of GnRF analog-DT conjugate in each edible tissue of swine are 0.264 ppm for muscle, 0.792 ppm for liver, 1.584 ppm for kidney, 1.584 ppm for fat, and 1.320 ppm for the injection sites.

## D. Residue Chemistry

1. Summary of Residue Chemistry Studies

   Traditional residue chemistry studies were not conducted for this supplemental approval. Due to the instability of GnRF analog-DT conjugate, a peptide protein conjugate, in swine, the Agency considered traditional residue chemistry studies inappropriate for the determination of incurred drug residue concentrations or metabolic profiles in gilts intended for slaughter. The Agency conducted a worst-case assessment to estimate the concentrations of the total GnRF analog-DT conjugate residues in the edible tissues, including the injection site, of gilts treated with Improvest®. If the estimated concentration of the total residues in an edible tissue is lower than the residue safe concentration for that tissue, then the residues in the edible tissue resulting from the treatment would not raise any human food safety concerns.

   The assessment assumes that, at the nominal zero withdrawal (8-12 hours post-treatment), the entire administered dose is distributed and then retained in each of the edible tissues including remote muscle, liver, kidney, and fat, and in 500 grams of the injection site muscle. In reality, drug absorption, distribution, metabolism, and elimination would take place after the administration, resulting in reduction of the drug residues to the concentrations less than those predicted in the worst-case assessment.

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

**A Worst-Case Assessment for Total Residues of GnRF analog-DT conjugate in Liver, Kidney, Muscle and Fat**

The assessment assumes that an average market-size gilt weighs 129 kg, and the liver, kidney, muscle, and fat of the pig make up 1.3, 0.3, 60.63, and 25 percent, respectively, of the body weight. The assessment also assumes that the entire 400 µg GnRF analog-DT conjugate dose is distributed to each of the four edible tissues and no drug residues are eliminated from the tissues (representing zero hours post-treatment). The resulting total residue concentrations in the tissues are shown in Table IV.1 below:

Table IV.1. Results of a Worst-Case Assessment for Total Improvest® Residues in Muscle, Liver, Kidney and Fat.

| Edible Tissues | Tissue Weight as of Live Market Size Pig of 129 kg | Tissue Weight Estimated (kg) | Concentration of Total Residues in Edible Tissue[1] (µg/g) | Human Exposure to Total Residues in Edible Tissue[2] (µg/person/day) |
|---|---|---|---|---|
| Muscle | 60.63% | 78.2 | 0.005 | 1.5 |
| Liver | 1.3% | 1.68 | 0.24 | 24.0 |
| Kidney | 0.3% | 0.39 | 1.03 | 51.5 |
| Fat | 25.0% | 32.25 | 0.012 | 0.6 |

[1]Calculated by dividing 400 µg GnRF analog-DT conjugate by the respective tissue weight estimated (kg).
[2]Calculated by multiplying the concentrations of total GnRF analog-DT conjugate residues with the respective food consumption factors (muscle, 300 g; liver, 100 g; kidney, 50 g; fat, 50 g).

*Conclusion:* The concentrations of total GnRF analog-DT conjugate residues in muscle, liver, kidney, and fat are below the respective safe concentrations for the edible tissues and do not raise human food safety concerns at zero withdrawal.

**A Worst-Case Assessment for Concentration of Total GnRF Analog-DT Conjugate Residues at the Injection Site**

A worst-case assessment for the concentration of total GnRF analog-DT conjugate residues at the injection site based on the treatment dose of 400 µg GnRF analog-DT conjugate is described below:

400 µg/500 g = 0.8 µg/g

Where: 500 g is the standard amount of injection site muscle collected for measuring residue concentrations at the injection site.

*Conclusion:* At zero withdrawal, the concentration of total GnRF analog-DT conjugate residues at the injection site is below the safe concentration for the injection site and does not raise human food safety concerns.

2. Target Tissue and Marker Residue

   It is not necessary to assign a target tissue or marker residue for residues of GnRF analog-DT conjugate in the edible tissues of swine.

3. Tolerance

   A tolerance for residues of GnRF analog-DT conjugate is not required in the edible tissues of swine. A tolerance is not required because a worst-case assessment demonstrated that the concentrations of total GnRF analog-DT conjugate residues in the edible tissues and injection site at zero withdrawal are below the respective safe concentrations for the edible tissues and injection site.

4. Withdrawal Period

   Based on the assessment summarized under Section IV.D.1 above, a 0-day withdrawal period is assigned for the use of Improvest® in gilts intended for slaughter.

### E. Analytical Method for Residues

Because a tolerance for residues of GnRF analog-DT conjugate is not required in the edible tissues of swine, an analytical method is not required.

## V. USER SAFETY

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

**Warning for person administering IMPROVEST:** Accidental self-injection could affect reproductive physiology of both men and women and may adversely affect pregnancy and fertility. **Pregnant women should not administer this product. Women of childbearing age should exercise extreme caution when handling this product.** Special care should be taken to avoid accidental self-injection and needle stick injury when administering the product. Protective clothing including, but not limited to, safety glasses and gloves should be worn. Use a safety injector, preferably one which has a dual safety system providing both a needle guard and a mechanism to prevent accidental operation of the trigger. In case of eye contact, rinse immediately with copious amounts of water. In case of skin contact, wash immediately with soap and water. The product should be stored safety out of the reach of children. As a reminder, it is the prescribing veterinarian's responsibility to inform drug administrators of the user safety warnings associated with IMPROVEST.

**Advice to the user in the event of accidental self-injection:** In the event of accidental self-injection, wash the injury thoroughly with clean running water. Seek prompt medical attention and take the package leaflet with you. Do not administer the product, and/or any other product with a similar action, in the future.

**Advice to the physician:** Accidental self-injection could affect reproductive physiology of both men and women and may adversely affect pregnancy and fertility. If self-injection with IMPROVEST is suspected, reproductive physiology should be monitored by assay of testosterone or estrogen levels (as appropriate).

The risk of physiological effect is greater after a second or subsequent accidental injection than after a first injection. The patient should be advised not to administer IMPROVEST, and/or any other product with similar action, in the future.

## 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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Improvest®, when used according to the label, is safe and effective for the temporary suppression of estrus in gilts intended for slaughter. Additionally, data demonstrate that residues in food products derived from species treated with Improvest® will not represent a public health concern when the product is used according to the label.

### A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian. Adequate directions for lay use cannot be written because professional expertise is required to properly administer the injection and due to the potential impact on human reproductive function if self-injected.

### B. Exclusivity

This supplemental approval for Improvest® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to gilts intended for slaughter.

### C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

### D. Patent Information

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