IMPROVEST- gonadotropin releasing factor analog-diphtheria toxoid conjugate solution
Zoetis Inc.

Improvest®

(gonadotropin releasing factor analog-diphtheria toxoid conjugate)
0.2 mg/mL
Sterile Solution for Injection

CAUTION

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

IMPROVEST (gonadotropin releasing factor analog-diphtheria toxoid conjugate) is a sterile solution for subcutaneous injection. Each mL contains 0.2 mg gonadotropin releasing factor analog-diphtheria toxoid conjugate, 150 mg of diethylaminoethyl-dextran hydrochloride, 1 mg chlorocresol, sodium hydroxide as needed to adjust pH and water for injection.

INDICATIONS FOR USE

INDICATIONS FOR USE: For the temporary immunological castration (suppression of testicular function) and reduction of boar taint in intact male pigs intended for slaughter.

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

DOSAGE AND ADMINISTRATION

IMPROVEST should be administered via subcutaneous injection into the post auricular region of the neck. A safety injector should be used, preferably one which has a dual safety system providing both a needle guard and a mechanism to prevent accidental operation of the trigger. The bottle is to be punctured by a vaccinator spike. Use bottle within 28 days of first puncture and puncture a maximum of twice. Each intact male pig or gilt should receive two 2-mL doses of IMPROVEST. 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. For reduction of boar taint, intact male pigs should be slaughtered no earlier than 3 weeks and no later than 10 weeks after the second dose. In case of misdosing, the animal should be re-dosed immediately

CONTRAINDICATIONS

Do not use IMPROVEST in intact male pigs or gilts intended for breeding because of the disruption of reproductive function.
Not approved for use in barrows, cull boars, or sows

WARNINGS AND PRECAUTIONS

WITHDRAWAL PERIODS:

No withdrawal period is required when used according to labeling.

Not for Human Use. Keep Out of Reach of Children.

USER SAFETY WARNINGS:

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 safely 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 a 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 a similar action, in the future.

To report suspected adverse events, for technical assistance, or to obtain a copy of the safety data sheet (SDS), contact Zoetis 1-888-963-8471.

For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

ANIMAL SAFETY WARNINGS AND PRECAUTIONS

Subcutaneous injection in intact male pigs and gilts can cause a transient local injection site reaction that may result in trim loss at slaughter.

ADVERSE REACTIONS

Preapproval Experience: The field study observations from field effectiveness studies were consistent with the observations made during the target animal safety studies of transient inflammation at the injection sites. IMPROVEST did not cause unusual clinical signs or an unexpected frequency or severity of injection site reactions, apart from the mild anaphylactoidtype reactions immediately following the first injection. Otherwise adverse events, as reported, were not uniquely attributable to IMPROVEST.

Postapproval Experience: (December 2013) The following adverse events are based on voluntary, post approval reporting in male pigs. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product

exposure using these data. In some cases anaphylactoid / anaphylactic-type reactions have been observed within a few minutes after the first administration of IMPROVEST with duration up to 30 minutes. Clinical signs may include dyspnea, cyanosis, ataxia, emesis or hypersalivation. Most animals recovered. In some cases, death has been reported as an outcome.

TARGET ANIMAL SAFETY:

Margin of Safety

The safety of two doses of IMPROVEST was evaluated in intact male swine. Thirty 9-week old intact boars received two subcutaneous doses of IMPROVEST in the same location 14 days apart. The boars received one of three treatments: Saline Control (12-mL), IMPROVEST at the intended dose (2-mL, 1X), or IMPROVEST at 6 times the intended dose (12-mL, 6X).

Boars were clinically monitored daily. In addition, observation and measurement of injection sites, body weight, quantitative feed consumption, hematology, and clinical chemistry analyses were also obtained. A complete postmortem examination was conducted on each boar 14 days after the second injection. IMPROVEST, administered subcutaneously at the label dose (2-mL) resulted in mild transient injection site reactions at the 1X dose and caused clinical signs of systemic inflammation at 6X the intended dose.

The signs of inflammation included depression, stiffness of the neck lasting up to five days, reduction in feed intake, and lower body weights. Multiple swollen joints and associated lameness, which may be signs of systemic inflammation, were observed in one 6X boar. Evaluation of blood work revealed increased white blood cell counts (eosinophilia and eutrophilia);
slight increases in total serum protein (above normal reference range in 50% of the 6X boars) and globulin (above the normal reference range in 40% of the 6X boars); and slight decreases in serum albumin in 6X boars. Injection sites for the 6X boars showed clinically detectable firmness persisting in all animals for 14 days after the second injection. Pain and sensitivity at the injection site persisted for up to five days, and erythema and heat were more prominent in the 6X boars than in the 1X boars. Mild to moderate chronic inflammation and discoloration in the subcutaneous tissues at the injection site were observed. In all IMPROVEST treated boars, atrophy of testes, prostate, and bulbourethral glands were observed as expected consequences associated with the intended effect of the drug. At the label 2-mL dose, IMPROVEST may cause transient injection site inflammation.

Injection Site Safety

Injection site safety was evaluated following the injection of IMPROVEST into healthy 17-week old boars. The treated boars received two 2-mL doses of IMPROVEST into the same injection site location 28 days apart, while the control boars received saline. Daily monitoring included clinical evaluation and observation and measurement of injection sites. Two days after the second injection, postmortem observations of injection sites were conducted. All clinical signs of observable injection site swelling were resolved within 24 hours, and pain on palpation resolved by 48 hours post-injection. Firmness persisted for up to 11 days after the first injection in 10% of boars. Gross injection site alterations consisted of subcutaneous edema with tan or red discoloration. Two 2-mL injections of IMPROVEST, administered 28 days apart into the same location resulted in transient injection site reactions following each injection and resulted in discoloration of tissue at the injection site which was observable approximately 48 hours after the second injection.

Field Safety

During the conduct of the nine location field effectiveness study in male pigs, IMPROVEST did not cause unusual clinical signs or an unexpected frequency or severity of injection site reactions. The field safety observations from this study were consistent with the observations made during the target animal safety studies of transient inflammation at the injection sites. Adverse events, as reported, were

not uniquely attributable to IMPROVEST. Similarly, during the conduct of field effectiveness studies in gilts, IMPROVEST did not cause unusual clinical signs or an unexpected frequency or severity of injection site reactions.

EFFECTIVENESS

IMPROVEST is an injectable sterile solution containing an incomplete analog of natural gonadotropin releasing factor (GnRF) conjugated to diphtheria toxoid in an adjuvanted formulation. Immunization with a two dose regimen of IMPROVEST, with a four week interval between doses, stimulates the pig's immune system to produce antibodies which can neutralize its own GnRF. Pigs given an initial dose of IMPROVEST are immunologically primed but do not produce sufficient antibodies to have any physiological effect. Following receipt of the second dose, the pig's immune system responds with a strong antibody response. These antibodies bind to and neutralize circulating GnRF in the bloodstream. Neutralization of GnRF blocks the hypothalamic-pituitarygonadal endocrine axis, thereby temporarily suppressing gonadal function, including both sex hormone production and reproductive capability in intact males; and temporarily suppressing estrus in gilts.

In male pigs, evidence of temporary immunological castration was provided in a series of studies showing that within 1-2 weeks after the second injection of IMPROVEST, anti-GnRF antibody levels increase significantly. With this rise in anti-GnRF antibodies, the levels of gonadal sex hormones were substantially reduced, the size of the testes, and spermatogenesis suppressed, as was the expression of typical male behaviors (aggression and sexual, e.g., mounting). Full immunological castration (suppression of testicular function) was demonstrated to last from 3 to 10 weeks after the second dose.

IMPROVEST injected boars will start to return to full reproductive function at a variable period after this time, as evidenced by increases in male sex hormones, testicle size, and intact male behavior.

Evidence to assess the acceptability of pork from IMPROVEST treated male pigs was provided through a series of consumer taste panels using consumers deemed sensitive to the taste of "tainted" meat. The presence of boar taint was evaluated on the basis of pork aroma and flavor and not by chemical analysis. Four consumer taste panel studies were conducted to demonstrate the difference of pork generated from IMPROVEST treated boars and intact boars. A surgically castrated male group was not evaluated during these studies. In these four studies, 767 sensitive consumers evaluated cooked pork loin samples from IMPROVEST treated and intact boars. These pigs were raised to market weight, injected with IMPROVEST as per product labelling and slaughtered 3 to 10 weeks after receipt of the second IMPROVEST injection. The consumers found the aroma and flavor of pork from the IMPROVEST injected pigs to be more acceptable than from the intact boars in all four studies.

In gilts, evidence of temporary suppression of estrus was provided in several studies showing that after the second injection of IMPROVEST, anti-GnRF antibody levels increased significantly, the weight of the ovaries was significantly decreased, and the percentage of gilts with visible follicles was low. In a study specifically evaluating estrus detection (standing response in the presence of a mature boar), IMPROVEST was effective in suppressing estrus from 2 weeks to 10 weeks after the second dose

STORAGE INFORMATION

Store under refrigeration at 2°-8°C (36°-46°F). Once broached, product may be stored under refrigeration for 28 days. Store bottle in carton until used. Protect from light. Protect from freezing.

HOW SUPPLIED

IMPROVEST is available in a 250 mL bottle.

Approved by FDA under NADA # 141-322

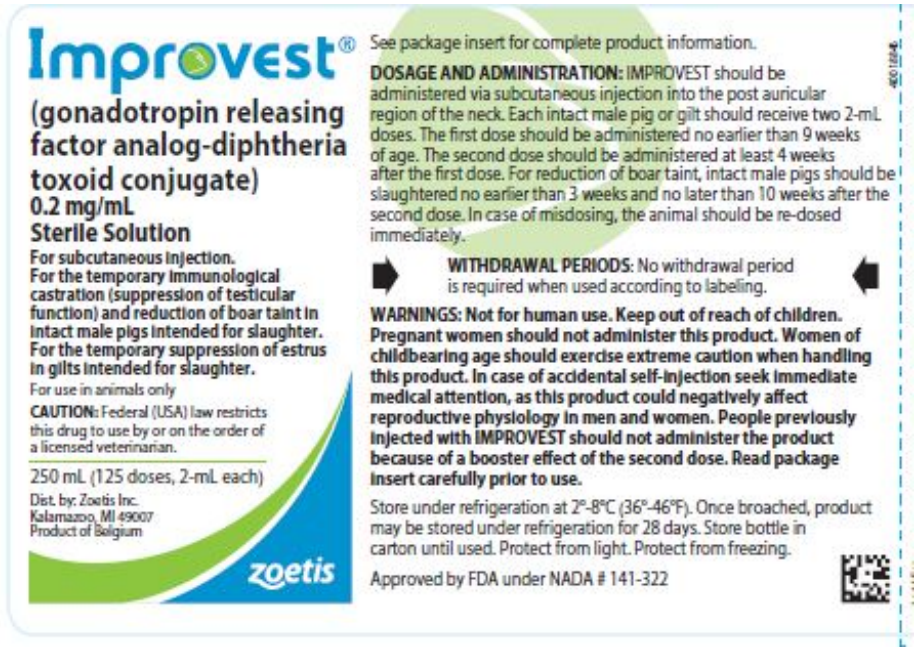
zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: January 2020

40018847

PRINCIPAL DISPLAY PANEL - 250 mL Bottle Label



IMPROVEST

gonadotropin releasing factor analog-diphtheria toxoid conjugate solution

Product Information			
Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:54771-1534
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GONADOTROPIN RELEASING FACTOR ANALOG-DIPHTHERIA TOXOID CONJUGATE (UNII: 1DBT5N7G0X) (GONADORELIN - UNII:9O7312W37G)	GONADOTROPIN RELEASING FACTOR ANALOG-DIPHTHERIA TOXOID CONJUGATE	0.2 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DIETHYLAMINOETHYL-DEXTRAN HYDROCHLORIDE (UNII: 85AMG1WQ9L)	150 ug in 1 mL

CHLOROCRESOL (UNII: 36W53O7109)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54771-1534-3	250 mL in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141322	10/01/2011	

Labeler - Zoetis Inc. (828851555)

Revised: 5/2020 Zoetis Inc.