

For those who grow and raise pigs

IMPROVEST®: KNOW THE FACTS

Pfizer Animal Health is committed to advancing the quality of pig care to create environmental, economic and social benefits around the world.



WHAT IS IMPROVEST AND HOW DOES IT WORK?

IMPROVEST (*gonadotropin releasing factor analog–diphtheria toxoid conjugate*) is a veterinary prescription product that is a **safe and effective alternative to surgical castration** to manage unpleasant aromas that can occur when cooking pork from some male pigs. It's a **protein compound that works like an immunization** to protect against these off odors.

FDA-approved, IMPROVEST is for the temporary immunological castration and reduction of boar taint in intact male pigs intended for pork. It's a protein compound that uses the pig's own immune system to provide the same effect as surgical castration, but much later in the male pig's life.

IT'S EFFECTIVE

IMPROVEST is as effective as surgical castration.¹ A related global brand, IMPROVAC®, has been used successfully by farmers in some countries for **more than 10 years**.

SAFE, QUALITY MEAT

Pigs raised using IMPROVEST produce the **same high quality pork** (free from unpleasant odors) **consumers enjoy today**.¹ The U.S. Food and Drug Administration has determined that meat from pigs given IMPROVEST is **safe to eat**. Regulatory authorities in 58 other countries, including the European Union and Japan, have reached the same conclusion for the related global brand, IMPROVAC.

CAPTURE MORE VALUE BY GROWING INTACT MALES

Male pigs are given IMPROVEST later in the finishing phase to manage off odors, eliminating the need for surgical castration. As a result, they're able to **grow to their full intact male potential**, with all the inherent advantages, until the second dose. Advantages documented in global studies include:

- **Improved feed efficiency** – Studies show a 6 to 10 percent improvement in feed efficiency.²
- **Increased cutout yield** – Studies also show a 2 to 2.5 percent increase in cutout yield.³
- **Reduced piglet mortality** – Since male pigs given IMPROVEST are not surgically castrated, the **risk of infection or death is eliminated**, decreasing mortality by 1.6 percent.⁴ Traditional complications associated with scrotal hernias, incision healing complications, low viability animals and cryptorchids would also be eliminated with the use of this immunological approach to manage boar taint vs. surgical castration. In addition, pigs given IMPROVEST are also less aggressive than intact males, behaving similarly to barrows.^{1,5}

• Decreased carbon footprint –

The production efficiencies gained by allowing male pigs to grow longer as intact males means they eat less feed and create less waste, which has the **potential for an incremental reduction in carbon footprint** by as much as 3.6 percent (measured in CO₂ equivalent per kilogram of pig live weight) vs. barrows.⁶ If half the male pigs in the United States were raised using IMPROVEST, it would be like removing the CO₂ equivalent of 130,000 cars for a year from our roads.^{6,7}

With the need to feed a growing world population, this approach has the potential for greater protein production with the use of fewer resources.

IMPACT ON THE ENVIRONMENT

The environment is of significant importance to the pork industry and its customers.⁸ The environmental impact of U.S. pork production is relatively low (0.33 percent of the total U.S. greenhouse gas emissions).⁹ Incremental reductions in these emissions remain a high priority.

As part of the overall commitment to help farmers further reduce greenhouse gases, Pfizer Animal Health has sponsored and had validated by a **third party an ISO-compliant global Life Cycle Assessment** for the related global brand IMPROVAC. The LCA measured the environmental impact of allowing pigs to grow longer as intact males with IMPROVAC. The assessment concluded that this approach has the **potential for an incremental reduction in the carbon footprint** vs. barrows.⁶

A COORDINATED FOOD CHAIN EFFORT

Use of IMPROVEST requires change and coordination throughout the pork value chain.

First, it means growing intact males. As the product is introduced, Pfizer Animal Health will work with veterinarians and their producer clients to help them adopt new nutritional guidelines and best handling practices to optimize growth for intact males. Product availability will increase gradually as the experience of working with intact males expands.

Second, this gradual approach also provides the time needed to ensure a coordinated food chain effort and gives packers and processors time to integrate and optimize this into their systems, as well. The goal is to have the best IMPROVEST program experience for everyone – from producers to meat packers and processors, retailers and, ultimately, to consumers.



www.PfizerPork.com/IMPROVEST



Improvest®

(Gonadotropin Releasing Factor Analog-Diphtheria Toxoid Conjugate, 0.2mg/mL)

FREQUENTLY ASKED QUESTIONS

Q Why IMPROVEST?

A IMPROVEST gives you a **safe and effective alternative to surgical castration** to manage boar taint. Meat from male pigs can have an offensive smell when cooked. While these naturally developing odors are completely safe, research shows that a high proportion of consumers, especially women, can easily detect them,^{10,11} making their control a necessity to protect the quality experience of eating pork.

Q What is it and how does it work?

A This FDA-approved product is a **protein compound that works like an immunization**, using the pig's own immune system to temporarily provide the same effect as surgical castration, but much later in the male pig's life. About a month before going to market, male pigs are given IMPROVEST, which stimulates their immune system to prevent them from producing the off-odor substances.

It's important to realize that IMPROVEST is **NOT a hormone** or growth promotant. It's **not added to the feed or genetically modified**. And, it is **not chemical castration**. It's a protein compound that creates a temporary immune response to manage the unpleasant aromas of boar taint.

Q Who benefits from the use of IMPROVEST?

A For farmers, IMPROVEST offers a safe and effective alternative to surgical castration of male pigs to reduce off odors in cooked pork.¹ By eliminating the need for surgical castration, the animals grow with all the inherent advantages of intact males. They convert feed to meat more efficiently, and the risk of piglet mortality associated with surgical castration is eliminated. Studies also show that following administration of IMPROVEST, pigs are less aggressive than intact males, behaving similarly to barrows.^{1,5}

For Americans who eat pork, you can enjoy the same high quality pork with the knowledge that it was raised using fewer resources. As intact males, they grow to more of their full intact male potential – converting feed into meat more efficiently. That means they eat less feed, create less manure, and produce more pork.^{2,3} Less waste and more pork means an incremental reduction in the carbon footprint compared to barrows.⁶

Q Is this technology used in other countries?

A Yes. This type of immunological technology is **approved in 58 other countries around the world**, including the European Union, Australia and Japan, under the related global brand, IMPROVAC. IMPROVAC has been used successfully by farmers in some countries for more than 10 years.

Q How is IMPROVEST given to pigs?

A IMPROVEST is administered via injection at the base of the pig's ear, and is not added to the pigs' feed. IMPROVEST is protein based and must be given as two injections to create the immunologic response needed to control the unpleasant aromas.

Q Is IMPROVEST a hormone?

A No. It's a protein compound that works like an immunization and has **absolutely no hormonal activity**. It uses the pig's own immune system to temporarily provide the same effect as surgical castration to manage substances that can cause unpleasant aromas in pork from male pigs.

Q Is it chemical castration?

A No. IMPROVEST is an immunological product, meaning it uses a pig's natural immune system to temporarily reduce the substances that cause the unpleasant aromas in pork.

Q Is it safe, are there residues in the meat?

A It is safe. There are **no residues in the meat from IMPROVEST that could affect human health**, according to the FDA. In its approval of IMPROVAC (related global brand), the European Union's regulatory authority stated that meat from pigs given IMPROVAC "would not contain any potentially harmful residues" and that the consumption of pork from these pigs therefore "poses no risk to the consumer."¹²

Q Why must I wait between four to eight weeks after the second dose to market my pigs?

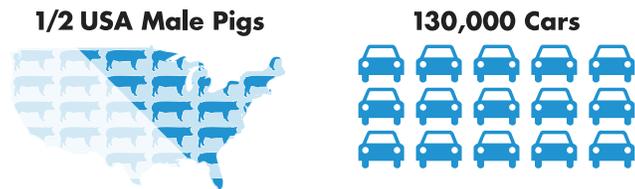
A That allows time for the pig's natural substances (androstenone and skatole) that cause the unpleasant aromas to clear the pig's system to ensure a high quality pork eating experience. That's why the label says pigs should not be sent to market prior to four weeks after the second dose, allowing adequate time for the reduction in the substances responsible for off odors in pork. Marketing pigs on the IMPROVEST program more than eight weeks after the second dose may increase the risk of odors in the pork.

Q Can this product be used on any size farm?

A Yes, this product is size-neutral. IMPROVEST can be used by, and brings benefits to, any size farm.

IMPROVEST	
IS	IS NOT
A protein compound	A hormone
An immunological product	Chemical castration
Temporary effect	Genetically modified
Uses the pig's own immune system	A growth promotant
Subcutaneous injection	Added to feed

If half the male pigs in the United States were raised using IMPROVEST, it would be like removing the CO₂ equivalent of 130,000 cars for a year from our roads.^{6,7}



Q How will raising intact males affect management practices on my farm?

A Use of IMPROVEST requires a significant change because intact male pigs have different nutritional requirements, which brings new management considerations.

As the product is introduced, Pfizer Animal Health will work with veterinarians and their producer clients to help them **adopt new nutritional guidelines and best handling practices to optimize growth for intact males on the IMPROVEST program.**

Product availability will increase gradually as the experience of working with intact males expands. This gradual approach also provides the **time needed to ensure a coordinated food chain effort and gives packers and processors** time to integrate and optimize this into their systems, as well.

Pfizer Animal Health wants to ensure the best IMPROVEST program experience for everyone – from farmers to meat packers and processors, retailers and, ultimately, to consumers.

Q How does this impact the environment?

A The efficiencies gained by allowing male pigs to grow longer as intact males before IMPROVEST is administered has the potential for an **incremental reduction in the carbon footprint.**⁶

The environment is of significant importance to the pork industry and its customers.⁸ The environmental impact of U.S. pork production is relatively low (0.33 percent of the total U.S. greenhouse gas emissions).⁹ Incremental reductions in these emissions remain a high priority.

Q Can I use this with other types of pigs?

A IMPROVEST should not be used with female pigs, barrows or male pigs intended for breeding.

Q What is gonadotropin releasing factor analog-diphtheria toxoid conjugate?

A It's the generic name for the active ingredient in IMPROVEST. Let's break it down:

1. Gonadotropin releasing factor analog –

Gonadotropin releasing factor, or GnRF, is a compound that all mammals produce naturally as they mature, including pigs. IMPROVEST does not contain the naturally occurring GnRF but rather it contains an incomplete version of it i.e., an analog, which makes it inactive.

2. Diphtheria toxoid (DT) – This is the same as the standard diphtheria vaccine that has been safely used in global childhood vaccination programs since the 1930s. It is simply a protein that contains natural amino acids. It is used as the carrier (conjugate) protein for the incomplete GnRF analog molecule.

3. Conjugate – Means “to join together.” The two compounds need to be joined together i.e., conjugated, to produce the immunological response in the pig. Together, they act as an immunization to control the substances that create the unpleasant aromas that can occur in pork from male pigs.

Q What are the most important safety considerations for IMPROVEST?

A Special care should be taken to avoid accidental self injection during administration of IMPROVEST. Accidental self injection could negatively affect reproductive physiology of both men and women. Therefore, pregnant women should not administer IMPROVEST and women of childbearing age, as well as men, should exercise extreme caution when administering the product. **There is no risk, however, of these effects on an individual who consumes pork from pigs given IMPROVEST.**

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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 is a sterile solution containing Gonadotropin Releasing Factor Analog-Diphtheria Toxoid Conjugate. 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: IMPROVEST is indicated for the temporary immunological castration (suppression of testicular function) and reduction of boar taint in intact male pigs 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. Each intact male pig 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. Pigs should be slaughtered no earlier than 4 weeks and no later than 8 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 intended for breeding because of the disruption of reproductive function. Not approved for use in female pigs and barrows.

WARNINGS:

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. **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. 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.

For customer service, to report suspected adverse reactions or to obtain a copy of the Material Safety Data Sheet (MSDS) call 1-800-336-5288.

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

ADVERSE REACTIONS: 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. Adverse events, as reported, were not uniquely attributable to IMPROVEST.

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 neutrophilia); 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, 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.

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-pituitary-gonadal endocrine axis, thereby suppressing testicular function, including both sex hormone production and reproductive capability, thereby providing temporary immunological castration in these injected boars.

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 was demonstrated to last from 4 to 8 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. IMPROVEST should not be used in boars intended for breeding purposes.

Evidence to assess the acceptability of pork from IMPROVEST treated 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. Three consumer taste panel studies were conducted to demonstrate the difference of pork generated from IMPROVEST treated and intact boars. A surgically castrated male group was not evaluated during these studies. In these three studies, 465 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 labeling and slaughtered 4 to 8 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 three studies.

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

HOW SUPPLIED: IMPROVEST is available in the following package sizes: 20 mL bottle, 100 mL bottle, 250 mL bottle, 500 mL bottle.

NADA # 141-322, Approved by FDA

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 **Pfizer Animal Health**

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