**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 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's safety studies of transient inflammation at the injection sites reacted 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 arthritis, 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 detected 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 at the subcutaneous tissues at the injection site were observed. In all IMPROVEST treated boars, atrophy of testicles, 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 on both sides of the neck, 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 site 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 significantly. With this rise in anti-GnRH antibodies, the levels of gonadotropin 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 increased in male sex hormones, testis size, and intact male behavior.

**Effectiveness:** IMPROVEST is an injectable sterile solution containing an incomplete analog of natural gonadotropin releasing factor (GnRH) 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 GnRH. 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. Antibody titer to GnRH and GnRH homologous bodies bind to and neutralize circulating GnRH in the bloodstream. Neutralization of GnRH blocks the hypothalamic-pituitary-gonadal 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-GnRH antibody levels increase significantly. This rise in anti-GnRH antibodies, the levels of gonadotropin 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 increased in male sex hormones, testis 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 tests 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. The value of these two studies was significantly higher, and the percentage of pigs with visible follicles was low. In a study specifically evaluating estrus detection (standing response in the presence of a mare 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

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**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:**

**Preappraisal 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 anaaphylactoid-type reactions immediately following the first injection. Otherwise adverse events, as reported, were not uniquely attributable to IMPROVEST.

**Postappraisal 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 anaaphylactoid / anaaphylactic-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.

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