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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for a type II variation for Improvac (EMEA/V/C/000136/II/0036)

International non-proprietary name: gonadotropin releasing factor analogue diptheria toxoid conjugate

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 25 January 2021 an application for a type II variation for Improvac.

Product name	**Application number and EU numbers**
Improvac	EMEA/V/C/000136/II/0036 - EU/2/09/095/002-003 and 005-006

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To modify the indication by adding the suppression of oestrus in female pigs and subsequent changes to the product information. Additionally, MAH is proposing to correct translation mistakes in different languages.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

Improvac is a vaccine against gonadotropin releasing hormone (GnRH). GnRH is a 10 amino acid-long peptide hormone, which is produced in the hypothalamus, and stimulates synthesis and release of follicular-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. In males as well as females, FSH and LH are the key gonadotrophic hormones which regulate testicular and ovarian development and function, with these endocrine mechanisms being highly conserved across mammals and indeed in most vertebrates (Esbenshade KL et al, J Reprod Fertil Suppl. 1990;40:19-32, and Whitlock KE et al, Front Neuroendocrinol. 2019 Apr;53:100738). Thus, inhibition of GnRH signalling, e.g. by immunisation against this self-antigen, causes hypothalamic hypogonadism and inhibits sexual maturation in males as well as females, across mammalian species.

The product consists of a synthetic peptide derived from the 10 amino acid long GnRH hormone, coupled to diphtheria toxoid (min. 300 ug/2 mL dose), adjuvanted with DEAE-dextran (300 mg/2 mL dose), with chlorocresol as the preservative (2 mg/2 mL dose, molar concentration 7 mM), formulated in water for injection.

This product is authorised in male pigs for the induction of antibodies against GnRH to produce a temporary immunological suppression of testicular function. For use as an alternative to physical castration for the reduction of boar taint caused by the key boar taint compound androstenone, in entire male pigs following the onset of puberty. Another key contributor to boar taint, skatole, may also be reduced as an indirect effect. Aggressive and sexual (mounting) behaviours are also reduced.

The onset of immunity (induction of anti-GnRH antibodies) can be expected within 1 week post second vaccination. Reduction of androstenone and skatole levels has been demonstrated from 4 to 6 weeks post second vaccination. This reflects the time needed for clearance of boar taint compounds already present at the time of vaccination as well as the variability of response between individual animals. Reduction of aggressive and sexual (mounting) behaviours can be expected from 1 to 2 weeks post second vaccination.

The applicant now proposes to expand product use to female pigs, to prevent unwanted pregnancies and sexual behaviour (standing oestrus) in gilts intended for slaughter.

The proposed variation is to include female pigs in indications: Induction of antibodies against GnRH to produce a temporary immunological suppression of ovarian function (suppression of oestrus) resulting in prevention of unwanted pregnancies in gilts intended for slaughter, and to reduce the associated sexual behaviour (standing oestrus).

Immunisation of female pigs with Improvac induces an immune response against endogenous gonadotrophin releasing factor (GnRH), a factor that controls ovarian function via the gonadotropic hormones, LH and FSH.

The effects of immunisation derive from the reduction in ovarian function resulting from reduced GnRH activity. This leads to reduced production and concentration of oestradiol and progesterone. Prevention of typical female behaviour (standing oestrus) and prevention of pregnancy can be expected from 1 to 2 weeks post second vaccination; prevention of pregnancy is particularly relevant in situations where fattening entire males and females are commingled.

Additionally, MAH is proposing to correct translation mistakes in different languages.

2.1. Safety

Two GLP-compliant, blinded, randomised, negatively controlled laboratory safety studies were conducted in 8-week-old female pigs with very similar design. In the first of the two studies, the needles used resulted in worse than expected local reactions, and therefore the study was repeated with other needles. Both studies were designed in accordance with relevant guidelines; included a relevant number of animals; used relevant endpoints; evaluated 3 repeated doses, which is one more than the intended use in the clinic; and used a batch with high potency. The age of the animals, however, is not in accordance with the draft SPC in which the minimum age is 14 weeks. Safety data from pivotal field studies conducted in Belgium and Spain, however, support that 14-week-old gilts overall have a similar safety profile of the TI as the 8-week-old gilts.

The female pigs in one of the studies showed higher transient temperature increases and more persistent local reactions than what is listed in the SPC for male pigs. The mean temperature increased

0.7 °C after the first injection with Improvac, and there was still histological evidence of local reactions in 67% of the pigs when the study was terminated 42 days after the first injection. Whether this reflects differences related to sex or to other factors such as the injection technique cannot be ascertained. In several pigs, myositis was found histologically, indicating that the injection was made intramuscularly rather than subcutaneously. Dosing intramuscularly is not in accordance with the SPC and could impact the safety due to differences in how the formulation distributes in the tissue, how fast it is absorbed, and how the tissue reacts with it. In the SPC, "it is recommended to use a shorter needle to give 5 mm to 9 mm penetration in undersized pigs and pigs younger than 16 weeks of age" to avoid intramuscular administration. The applicant suggested updates to the SPC to provide further guidance on how correct subcutaneous deposition can be achieved. In addition to the suggested changes, the applicant was invited to also consider amending the sentence "The needle should be directed perpendicular to the skin surface", as it is not clear for self-tenting devices. The applicant agreed with this and accepted to replace the sentence "*The needle should be directed perpendicular to the skin surface*" by the sentence "*Follow instructions for proper subcutaneous injection provided with the device used*."

To support the two GLP studies, a GCP-compliant, designed as a blinded, randomised, negatively controlled study was conducted to assess the safety and efficacy of Improvac in 18-week-old female crossbred Iberian pigs: 20 controls; 20 given 3 doses; and 20 given 4 doses (to assess efficacy until slaughter at 60 weeks of age, i.e. markedly later than typical slaughter pigs). In all groups, the first two doses were administered four weeks apart, and later doses 12 weeks apart. The Improvac batch had intermediate potency, which is acceptable in cases where safety has been adequately assessed under laboratory conditions. However, the usefulness of the study to document the safety of Improvac when used as intended according to the draft SPC is limited by a number of things: 1) No recordings were made of either feed intake or body weight; 2) The animals were not typical slaughter pigs, were fed ad libitum and were 4 weeks older than the minimum age in the SPC (14 weeks); 3) A longer needle than that described in the SPC was used, and no histological (or other) evaluations were made to document correct subcutaneous dosing; 4) The injection sites were only inspected clinically; 5) The investigator, who was not blinded relative to study group allocations, also evaluated clinical signs and injection sites, i.e. the key safety endpoints; 6) There was a number of inconsistencies with GCP compliance, some of which potentially impact the importance of the conclusions drawn regarding safety (e.g. unclear or illegible data capture forms, lack of blinding, and incorrect reporting of the body temperature increases).

Three pivotal field studies were designed and performed in commercial farms in Belgium, Spain and the United Kingdom through the period 2019-2021:

- Field study 1: Assessment of Safety and Efficacy of Improvac in Gilts from 14 Weeks of Age under Field Conditions in Belgium.
- Field study 2: Assessment of Safety and Efficacy of Improvac in Gilts from 8 Weeks of Age under Field Conditions in the United Kingdom.
- Field study 3: Assessment of Safety and Efficacy of Improvac in Gilts from 8 Weeks of Age under Field Conditions in Spain.

In all 3 pivotal field safety studies, the following safety observations were consistently made:

- Local injection site reactions were very common after immunisation with Improvac (seen in 5% to 70% of immunised animals).

- In a significant proportion of the cases where injection site reactions occurred (up 10% of injection site cases), they were quite pronounced, and appeared to cause irritation to animals (swellings 2 – 5 cm diameter, exhibiting cutaneous erythema or palpable subcutaneous or intramuscular swelling, accompanied by evidence of irritation such as persistent rubbing at injection site, but without exudates).
- In most cases, injection site reactions resolved within approx. 2-14 days, but in some cases persisted for up to 24 days.
- Increases in body temperature including fever (≥ 40.5 °C) up to 72h duration were very commonly observed at 4 hours after administration of the product.

Also, systemic allergic/anaphylaxis-like reactions (dyspnoea, vomiting) were observed in one gilt after the second immunisation with the product (5% of animals in treatment group).

Thus, in gilts, the product was strongly reactogenic (injection site reactions), to a degree which potentially impacted welfare in a significant proportion of vaccinated animals (evidence of irritation such as persistent rubbing at the injection site in up to 10% of cases of injection site reactions), and also triggered immediate systemic effects of immunological nature (transient fever very commonly, allergic reactions rarely).

The occurrence of injection site reactions after immunisation with the product varied between study sites: the lowest frequency and severity of product-associated injection site reactions were seen in study 2 and the highest frequencies and severities of product-associated injection site reactions were seen in studies 1 and 3.

This difference between study sites as regards severity of product-associated injection site reactions was also seen for the placebo treated groups (gilts injected subcutaneously with isotonic saline): in study 2, injections site reactions were not seen in placebo-treated gilts, while in studies 1 and 3, injections site reactions were common also in placebo-treated gilts, albeit at lower frequencies and severity than in gilts immunised with product.

Thus, the variability between the 3 study sites as regards frequency and severity of injection site reactions likely was at least partly due to differences in injection practices (training of staff) and potentially also general farm hygiene.

In this regard, it should be mentioned that in all 3 studies, the same safety injector and needle lengths were used [Sekurus Self-tenting injectors, SIMCRO, with 1.6 x 19 mm (16G x 3/4 '') needles], and in all 3 studies, injection sites were rotated such that the subcutaneous injections were never given at the same site of the neck two times in a row.

The severity of the local injection site reactions did not appear to correlate with the number of immunisations that gilts had received (pronounced injection site reactions could be seen already after the 1st immunisation and did not appear to increase in frequency after the 2nd immunisation).

However, regarding the interpretation of the potential relationship between the number of immunisations and severity of local injection site reactions, it should be stressed that as mentioned above, injection sites were rotated.

In the pivotal field studies, the effect of so-called early and late priming (first immunisation at 8 or 14 weeks of age) on product safety was examined.

However, due to the abovementioned difference in placebo-associated injection site reactions between studies 1 (high frequency of placebo-associated injection site reactions) and 2 (low frequency of

placebo-associated injection site reactions), the difference between these 2 studies regarding product-associated injection site reactions (high in study 1, low in study 2) cannot be interpreted as being due to the age at which animals were first immunised. In study 3, early and late priming immunisations were compared side-by-side. However, due to (i) the general variability of the data, and (ii) the relatively frequent occurrence of injection site reactions in the placebo group in study 3, the results from the study are also not considered to be conclusive as regards to whether certain age groups may be more sensitive to local injection site reactions after immunisation with the product.

Fever most likely reflects strong, general immune stimulation, which is expected for this product class (adjuvanted vaccine).

Further, the frequent occurrence of febrile reactions is not unexpected for this particular product, because the immunogen is short (synthetic peptide representing part of the GnRH hormone, which itself is only 10 amino acids long) and mimic a self-antigen against which immunological tolerance likely exists, both factors reducing immunogenicity of GnRH peptides to a degree which cannot be solved completely by coupling the GnRH peptides with carrier proteins (such as diphtheria toxoid in the present case), thus often additionally requiring the use of strong adjuvants (Oonk HB et al, Vaccine. 1998 16(11-12):1074-82 and Beekman NJ et al, Vaccine. 1999, 17(15-16):2043-50). Indeed, the DEAE-dextran adjuvant used in the product has been described as being of similar strength as Freund's incomplete adjuvant, one of the strongest adjuvants known (Finnerty M et al, J Reprod Fertil. 1994, 101(2):333-43 and Beh KJ et al, Immunology 1985 54(3):487-95).

As regards allergy/anaphylactoid reactions, the product contains chlorocresol as the preservative, and high molecular-weight DEAE-dextran as the adjuvant (500 kDa). Chlorocresol is known to be able to cause local as well as systemic hypersensitivity reactions (Hancock BW et al, Br Med J. 1975, 3(5986):746-7, Ainley EJ et al, Lancet. 1977, 1(8013):705, and Walker SL et al, Br J Dermatol. 2004 151(4):936-7), and dextran is also a known to be able to cause systemic anaphylaxis/anaphylactoid reactions (Zinderman CE et al, J Vasc Surg. 2006 43(5):1004-9). Thus, frequent febrile responses and rare anaphylactoid-type responses to immunisation with the product are expected, irrespective of animal age.

In summary, for the reasons above, the pivotal field safety studies do not specifically provide data as regards whether certain age groups may be more sensitive to local injection site reactions after immunisation with the product.

On the other hand, it is acknowledged that taken together, the 3 pivotal studies in combination bracket the gilt age at which product is intended to be used (gilts from 14 weeks of age onwards). Thus also, taking into consideration current scientific knowledge about the general safety of the type of product (adjuvanted, protein-based vaccine) and the specific composition of the product (protein immunogen adjuvanted with DEAE-dextran and added chlorocresol as preservative), the 3 pivotal field studies are considered to provide sufficient data to evaluate the safety of the product in the intended gilt age group (gilts from 14 weeks of age onwards).

Use during pregnancy or lay:

In the pivotal field safety studies, product use in pregnant animals was not explored. Yet, it is known that in addition to stimulating production and release of FSH and LH in the pituitary gland, GnRH also has extra-pituitary effects such as for example supporting embryonal development and maintenance of pregnancy (Nam DH et al, Theriogenology, 2005, 63(1):190-201), and it is likely that interruption of GnRH signalling during pregnancy may have adverse effects on placental and foetal viability (Siler-Khodr TM et al, Fertil Steril. 1984, 41(3):448-54).

In other words, as regards the pituitary effects of GnRH, immunisation with the product is known to have identical effects in males and females (hypothalamic hypogonadism and inhibition of sexual maturation), but as regards extra-pituitary effects of GnRH, immunisation with the product is expected to have different effects in males and females.

It seems warranted to reflect this in the SPC, by providing sex-specific safety-related guidance for product use.

Overall conclusion on safety

In conclusion, two laboratory safety studies were conducted in 8-week-old female pigs (pivotal study). Both were GLP compliant; included a relevant number of animals; used relevant endpoints; evaluated 3 repeated doses and used a batch with high potency. The age of the animals and the length of the needles used for injection, however, was not in accordance with the draft SPC. The age could influence the injection site anatomy, and regarding the needles, myositis was found histologically in several animals, indicating that several injections were made intramuscularly rather than subcutaneously. Apart from injection site reactions, the vaccinations did not cause systemic adverse reactions other than transient, mild temperature increases. The body temperature increases were higher, and the local reactions were more persistent than what is listed in the SPC for male pigs. The applicant has been asked to review the SPC with regard to these temperature increases.

To support the two GLP studies, a study evaluated 3 or 4 repeated doses of Improvac in 18-week-old female crossbred Iberian pigs slaughtered late (at 60 weeks of age). However, a number of weaknesses in the design and conduct of the study limits its usefulness to document the safety of Improvac when used as intended according to the draft SPC.

As detailed in the scientific overview section, the pivotal field studies do have shortcomings as regards documentation of product safety in gilts in the claimed age range (from 14 weeks of age). On the other hand, it is acknowledged that based on current scientific knowledge about the general safety of the product class (adjuvanted, protein-based vaccine) and the specific composition of the product (protein immunogen adjuvanted with DEAE-dextran and added chlorocresol as a preservative), the 3 pivotal field studies provide data to support the safety of the product in the intended gilt age group (gilts from 14 weeks of age onwards).

However, interpretation of the combined safety data available from male and female pigs is associated with complications, giving rise to some concerns. Due to the recognised extra-pituitary effects of GnRH in supporting pregnancy (please see details under scientific overview), it is likely that product use in pregnant animals may be associated with adverse outcomes for foetuses and/or dams; yet, safety in pregnant animals was not addressed in any of the studies. A warning against use in pregnant animals has been added in the SPC.

2.2. Efficacy

Fourteen studies were submitted in support for the efficacy of Improvac to suppress oestrus in gilts.

The products used were either Improvac in the European studies or Improvest in the studies in the USA and Canada. The dose was 2 ml given subcutaneously behind the ear. The number of doses given varied between studies from 2 to 4.

Pivotal efficacy study:

Assessment of the efficacy of two doses of Improvac in suppressing oestrus in young female pigs, administered from eight weeks of age.

In this pivotal study carried out on the company farms in Spain, Landrace × Large white crossbreed gilts were randomised to three groups with 18 (T01) or 19 pigs in each (T02, T03). They were immunised with Improvac either at 8 and 18 weeks of age (T02 "Early Priming" EP) or at 14 and 18 weeks of age (T03 "Late Priming" LP). Gilts in the control group (T03) were injected with 2 ml saline at 8, 14 and 18 weeks of age. The gilts of T02 and T03 were likewise sham vaccinated at 14 and 8 weeks of age, respectively. The vaccine was given at room temperature with a 16 G × ¾ inch (19 mm) needle using a Simcro Sekurus syringe. Study day 0 was the day of first (sham) vaccination. The pigs were euthanised at study day 126 (26 weeks of age). The Improvac batch had a potency close to the minimum potency.

The primary variable was the detection of standing oestrus at least once post-second injection beginning one week post second injection. The secondary variables were anti-GnRH antibodies, progesterone and oestradiol levels, reproductive tract weight, uterine horn length, number and size of ovarian follicles, body weight and average daily gain.

Gilts were tested for standing oestrus by the back pressure test in the presence of a teaser boar three times per week between study days 77 and 126 (19 and 26 weeks of age, respectively). Eighty three percent of the gilt in the control group (T01) showed standing oestrus at least once during the observation period, whereas significantly ($P<0.0001$) fewer gilts in the treatment groups showed standing oestrus (3 gilts (15.8%) in Early Priming group (T02) and none (0%) of the Late Priming group (T03)).

All pigs continuously gained weight during the study. No significant differences were detected in body weight between groups.

In blood samples collected at study days 0, 42, 70, 84, 98, 112 and 126, notable increased titres against GnRH were detected in the vaccinated gilts from two weeks after the second vaccination. In the un-vaccinated group, a notable increase in progesterone was seen with a peak in mean values at study day 112, whereas the values in the two treatment groups remained close to baseline. At the last study day an increase was seen in oestradiol concentrations of the control group, whereas the values in the treatment groups remained at baseline.

Mean uterine and ovarian weights at necropsy were significantly ($P<0.0001$) lower in the treatment groups than in the control group as were the lengths of the uterine horns. Ovaries were scored for follicle development (Scores: 0=No follicles; 1=Immature follicles, 3-4 mm; 2=Mature follicles, 8-11 mm; 3=Mature follicles and luteal tissue). Follicle number and size was lower in vaccinated groups compared to control gilts. In the Early Priming group (T02) three gilts had ovaries with score 2 or 3, whereas none of the gilts in the Late Priming group (T03) had follicles at this stage of development.

This study, where pigs were vaccinated either at 8 and 18 weeks of age (T02) or at 14 and 18 weeks of age (T03) and monitored for 8 weeks after the last vaccination, showed a reduction in sex hormones, uterus size, ovarian size and maturity, and occurrence of standing oestrus in both of the vaccinated groups (T02 and T03) although the highest reductions were seen in the group vaccinated at 14 and 18 weeks of age (T03). Total prevention of oestrus and absence of mature follicles was only seen following vaccination at 14 and 18 weeks of age (T03).

Two questions were raised to the applicant regarding the onset of protection and the duration of protection, respectively.

Two of the supportive studies were carried out in the EU on crossbred Iberian pigs.

- Evaluation of the safety and efficacy of Improvac in Suppressing Oestrus and Oestrus-related Behaviour in Entire Iberian Female Pigs in Spain, also published by Dalmau et al, 2015.

- Evaluation of the safety and efficacy of Vacsincel under field extensive conditions in Spain.

One of these studies was carried out on gilts raised indoors. In this study (also published by Dalmau et al. 2015) groups of 15 Iberian × Duroc crossbred gilts were vaccinated with Improvac at 18, 22, and 34 weeks of age (group V3), or at 18, 22, 34 and 46 weeks of age (group V4) and monitored until the end of the study at 60 weeks of age. A control group was injected with 2 ml PBS subcutaneously on the same occasions. The study was randomised and blinded.

Blood samples were taken in the study period at intervals of 2-4 weeks. Significant increases in anti-GnRH titres were seen after the second vaccination with Improvac and again after the third and fourth vaccinations. Serum titres declined notably between vaccinations.

Serum progesterone was also followed systematically, but not oestradiol. Both vaccinated groups (V3 and V4) had levels of progesterone close to baseline until the end of the study, whereas the mean progesterone values of the control group increased from study day 112. Mean progesterone values were significantly different between the vaccinated and control groups ($P < 0.0001$) from study day 112 (age approximately 32 weeks) until the end of the study.

Oestrus detection was performed systematically three times per week through detection of standing oestrus by back pressure in the presence of a teaser boar. Seventeen of 20 animals in the control group showed standing oestrus on at least one occasion. In treatment group V3, three of 20 animals showed standing oestrus on a single occasion whereas no gilts in the V4 group showed standing oestrus. At necropsy, 61% of the examined ovaries in the control group showed developing follicles in stage 2 or 3, whereas two ovaries (6%) in the V3 group were in stage 2 and developing follicles were absent in group V4.

A second field study was carried out in the same breed of gilts raised on free-range pasture in Spain. The study was of limited size (total of 30 pigs enrolled, 24 pigs at termination) and the pigs were not systematically monitored for oestrus. However, results from progesterone analysis and examination of reproductive organs at slaughter, supported efficacy when the Iberian pigs were dosed at 18, 22, 34 and 46 weeks of age and kept until approximately 60 weeks of age. Please note that the posology was different to the one proposed for Improvac.

This second field study was performed with the product Vacsincel. Vacsincel is indicated exclusively for female pigs raised under extensive (outside) conditions from 18 weeks of age to induce antibodies against GnRF to produce a temporary immunological suppression of ovarian function as an alternative to the physical castration in not allowing the animals to reach puberty. The product addresses the specific field situation in a single EU Member State for a relevant subgroup, gender and breed, of the target species pigs: Iberian females raised under extensive conditions and reaching older age and heavier body weight in Spain. This is reflected by a different administration schedule: four dose vaccination schedule from 18 weeks of age. Vacsincel is not approved in male pigs.

Three other **field studies** were carried out in the EU.

A study carried out in Belgium followed the proposed posology to administer Improvac at 14 and 18 weeks of age, and showed that oestrus and development of the reproductive organs were both significantly reduced for a 9-week period in the Improvac group, however without leading to a complete suppression in all gilts as some follicle development was seen at slaughter and two of 18 gilts entered oestrus before slaughter. The study generally showed efficacy after dosing at 14 and 18 weeks of age in terms of statistically significant difference between Improvac and Placebo groups for 9 weeks after the second vaccination.

The two studies using early priming at 8 weeks of age at first dosing did not provide support for this age for the first vaccination. In the UK study differences between vaccinated and control groups were minor, and in the Spanish study the gilts entered too late into puberty to evaluate the results.

Eight **supportive studies** were conducted in the USA, Canada, and Australia. They were mostly conducted on experimental pig facilities owned by the porcine industry, government or universities. These studies are presented either in the laboratory section or the field study section of the dossier, but there is no major difference between the "laboratory" and "field" studies. Therefore, they are presented together here.

Efficacy studies were randomised and blinded. Most studies were placebo-controlled, whereas the control group in a few studies was non-treated. Four of the studies were conducted according to GCP standards.

The age at vaccinations were not necessarily the same as the suggestion in the present application. The interval between first and second vaccination varied between 3 and 11 weeks.

Oestrus detection was performed systematically in one of the studies. Control for standing oestrus was performed daily by back pressure in the presence of a teaser boar. One gilt came in oestrus shortly after the second vaccination with Improvest, and the gilt was assumed to have entered oestrus before the onset of the effect of the product.

The effect on body weight gain, feed intake, feed conversion and carcass composition were determined in most of the supportive studies. These effects are not part of the present application and will not be commented upon further here.

Statistically significant reductions in oestradiol were found in three studies, which in one study was accompanied by a significant reduction in progesterone concentration.

At necropsy, ovaries and sometimes uterus were weighed and follicle development was scored. The studies showed consistently a reduced weight of ovaries and uterus in the vaccinated groups. Follicle development was likewise considerably less in the treated groups, but not all studies showed a complete absence of follicles in the later stage of development (stage 3 or 4) in the treated groups.

For some studies the follow-up observational period between the second vaccination and euthanasia was too short to realistically expect that all animals would have entered puberty.

These studies can be considered supportive of notable reductions of ovarian development, reductions in oestradiol and progesterone concentrations, and oestrus behaviour after a second dose of Improvac. It is noted that they were not performed with the same posology as the one suggested in the present application, and that the reductions, although statistically significant, were not always in the form of a complete cessation of ovarian activity at the end of the study periods.

Overall conclusion on efficacy

One well-conducted pivotal laboratory study showed that when gilts were vaccinated at 14 and 18 weeks of age, they showed a reduction in sex hormones, uterus size, and ovarian size and maturity for 8 weeks after the last vaccination. The occurrence of standing oestrus was prevented. One field study in Belgium used the same posology and showed that oestrus and development of the reproductive organs were both statistically significantly reduced for a 9-week period in the Improvac group, however without leading to a complete suppression of oestrus and ovarian development.

Two field studies were carried out with crossbred Iberian×Duroc gilts in Spain vaccinated at 18, 22, 34 and 46 weeks of age. These gilts were raised indoors in one study and on free-range pasture in the other study. Both studies supported that Improvac prevented sexual maturation in the field until the time of slaughter at approximately 60 weeks of age.

Questions were raised to applicant about the onset of protection, which is claimed from one week after second vaccination, and the duration, which has been claimed for 9 weeks. These values are not in complete agreement with the pivotal laboratory study.

The supportive studies carried out in the USA, Canada, Australia and Spain used different vaccination regimes compared with the variation proposed. After a second vaccination, they showed notable reductions of ovarian development, reductions in oestradiol and progesterone concentrations, and oestrus behaviour. These reductions, although significant, were not always in the form of a complete cessation of ovarian activity at the end of the study periods.

The benefit of the product under field conditions was discussed during the procedure. The most important benefit will be in terms of a reduction in the rate of unwanted pregnancies when female pigs are raised to an age above the age of puberty and housed with non-castrated male pigs. Additionally, the suppression of ovarian function will lead to less oestrus-related behavior, including aggressive behavior during oestrus.

3. Benefit-risk assessment of the proposed change

Improvac is authorised in male pigs for the induction of antibodies against GnRH to produce a temporary immunological suppression of testicular function. The proposed variation is to include female pigs in indications: Induction of antibodies against GnRH to produce a temporary immunological suppression of ovarian function (suppression of oestrus) resulting in prevention of unwanted pregnancies in gilts intended for slaughter, and to reduce the associated sexual behaviour (standing oestrus).

Immunisation of female pigs with Improvac induces an immune response against endogenous gonadotrophin releasing factor (GnRH), a factor that controls ovarian function via the gonadotropic hormones, LH and FSH. The active ingredient in this immunological is a synthetically produced analogue of GnRH, which is conjugated with an immunogenic carrier protein. The conjugate is adjuvanted to increase the level and duration of effect.

The effects of immunisation derive from the reduction in ovarian function resulting from reduced GnRH activity. This leads to reduced production and concentration of oestradiol and progesterone. Prevention of typical female behaviour (standing oestrus) and prevention of pregnancy can be expected from 1 to 2 weeks post second vaccination; prevention of pregnancy is particularly relevant in situations where fattening entire males and females are commingled.

3.1. Benefit assessment

Direct benefit

The proposed benefit of this product is to induce antibodies against GnRH to produce a temporary immunological suppression of ovarian function (suppression of oestrus) resulting in prevention of

unwanted pregnancies in gilts intended for slaughter, and to reduce the associated sexual behaviour (standing oestrus).

One well-conducted pivotal laboratory study showed that when gilts were vaccinated at 14 and 18 weeks of age, they showed a reduction in sex hormones, uterus size, and ovarian size and maturity for 8 weeks after the last vaccination. The occurrence of standing oestrus was prevented. One field study in Belgium used the same posology and showed that oestrus and development of the reproductive organs were both statistically significantly reduced for a 9-week period in the Improvac group, however without leading to a complete suppression of oestrus and ovarian development.

The supportive studies carried out in the USA, Canada, Australia and Spain used vaccination regimes different from the one proposed in the variation. After a second vaccination, they showed notable reductions of ovarian development, reductions in oestradiol and progesterone concentrations, and oestrus behaviour. These reductions, although statistically significant, were not always in the form of a complete cessation of ovarian activity at the end of the study periods.

The benefit under field use will be in terms of reduced rate of pregnancies in pigs intended for slaughter and a reduction in aggressive behavior in relation to oestrus. The benefit of the product will be in situations where female and intact male pigs are raised together after onset of puberty. This situation occurs as pigs are commonly raised to higher slaughter weight than seen previously, and there is a tendency to avoid physical castration of male pigs in some European countries. Likewise, the reduction in aggressive behavior in relation to oestrus is considered a benefit as the behavior may lead to fighting and injuries.

Additional benefits

Studies in the USA and Canada have demonstrated a positive effect on production parameters (growth and feed conversion). The pivotal efficacy study in this EU application did not find significant differences in body weight gain between treatments.

3.2. Risk assessment

Quality:

As no changes have been introduced in the product manufacturing, there are no quality concerns to be addressed here.

Safety:

Risks for the target animal:

In the pivotal safety studies, the general adverse event profile of the product in gilts was qualitatively similar to the safety profile previously described for the product in male pigs (local injection site reactions, temperature increases, and a few cases of anaphylactic-type reactions). However, concerns were raised that the injection site reactions could be more severe and persistent, the temperature increase could be higher, and the anaphylactic-type reactions could be more common in female than in male pigs.

The product contains a strong adjuvant which is also directly cytotoxic (DEAE-dextran) and is thus expected to be locally irritating. Indeed, local injection site reactions were very common after immunisation (seen in 5% to 70% of immunised gilts in pivotal field safety studies), and in a significant proportion of cases where injection site reactions occurred (up 10% of the injection site cases), they were quite pronounced, and appeared to cause irritation to animals (swellings 2 – 5 cm diameter, exhibiting cutaneous erythema or palpable subcutaneous or intramuscular swelling, accompanied by evidence of irritation such as persistent rubbing at injection site, but without exudates). Thus, use of the product has a clear impact on the welfare of treated animals.

Risk for the user:

The risk for the user is unchanged by this variation.

Risk for the environment:

The proposed use in gilts will not lead to new environmental concerns.

Risk for the consumer:

The proposed use in gilts will not lead to new concerns for the consumer.

Special risks:

3.3. Risk management or mitigation measures

Instructions for injection have been updated in the SPC with regard to needle length and the use of self-tenting safety injectors.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, environmental safety, user safety or consumer safety.

The overall benefit-risk evaluation for the product in the applied indication is at present positive.

Therefore, the CVMP considered that the data available would allow the Committee to conclude on a positive benefit-risk balance.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Improvac can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to modify the indication by adding female pigs and subsequent changes to the product information.

Additionally, MAH is proposing to correct past translation mistakes in different languages.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the abovementioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA and IIIB.

Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.9 and 5 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.