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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Improvac (EMEA/V/C/000136/VRA/0039/G)

Vaccine common name: gonadotropin releasing factor analogue diphtheria 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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 4 April 2022 an application for a group of variations requiring assessment for Improvac.

1.2. Scope of the variation

Variations requested	
G.I.18	One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

The group of variations is to extend the inter-dose interval from 4 to 8 weeks, and to reduce the minimum age of vaccination accordingly (from 14 to 10 weeks of age) in female pigs (G.I.4) and to update the product information according to QRD template version 9.0 (G.I.18).

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 and Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Improvac is an immunological product inducing antibodies against gonadotropin releasing factor (GnRF). GnRF is a 10 amino acid-long peptide, which is produced in the hypothalamus, and stimulates synthesis and release of follicular-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. FSH and LH are the two key gonadotrophic hormones, which regulate testicular and ovarian development and function in male and female mammals respectively. Thus, inhibition of GnRF signalling, e.g. by immunisation with 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 analogue to the 10-amino acid-long GnRF, coupled to diphtheria toxoid (min. 300 ug/2 mL dose), adjuvanted with DEAE-dextran (300 mg/2 mL dose), with chlorocresol as preservative (2 mg/2 mL dose, molar concentration 7 mM), formulated in water for injections.

The product is authorised in male and female pigs (gilts intended for slaughter) for the induction of antibodies against GnRF. In gilts this produces a temporary immunological suppression of ovarian function (suppression of oestrus) in order to reduce the incidence of unwanted pregnancies and to reduce the associated sexual behaviour (standing oestrus). The onset of immunity (induction of anti-GnRF antibodies) can be expected within 1 week post second vaccination. Reduction of sexual behaviour (standing oestrus) can be expected from 1 to 2 weeks post second vaccination. The duration of immunological suppression of ovarian function has been demonstrated for 9 weeks after the second vaccination in the previous presented variation package EMEA/V/C/000136/II/0036.

The applicant now proposes to extend the inter-dose interval from 4 to 8 weeks, and to reduce the minimum age of vaccination accordingly (from 14 to 10 weeks of age) in female pigs to provide more flexibility to the use as this is of practical importance in the pig industry. Additionally, this variation application also includes an update of the product information according to QRD template version 9.0.

Variation G.I.4. is to extend the inter-dose interval from 4 to 8 weeks, and to reduce the minimum age of vaccination accordingly (from 14 to 10 weeks of age) in female pigs.

The applicant would like to provide more flexibility to the immunisation interval and the age of first administration and has therefore conducted a new clinical study in which the efficacy of Improvac following an eight-week immunisation interval was evaluated. Widening the immunisation interval means that the first immunisation can be administered to gilts from 10 weeks of age and the second immunization 4 to 8 weeks later in order to achieve efficacy before the onset of sexual maturity (approximately 20 weeks of age) and until slaughter (approximately 26 weeks of age).

General requirements for such changes are given in EU Regulation 2019/6. Additional guidance is provided by the appropriate Ph. Eur. monographs "Vaccines for Veterinary Use (Ph. Eur. 0062)" and "Evaluation of Efficacy of Veterinary Vaccines and Immunosera (Ph. Eur. 50207)". Furthermore, the EMA "Guideline on requirements for the production and control of immunological veterinary medicinal products" (EMA/CVMP/IWP/206555/2010-Rev.2), and EMA "Guideline on clinical trials with immunological veterinary medicinal products" (EMA/CVMP/IWP/260956/2021). Additionally, the product information (PI) has been updated according to the new QRD v.9 template (Version 9, 071003/2022).

2.1. Safety

No new data was provided.

Overall conclusion on safety.

Safety remains unaffected by this variation as the risks for the user, consumer, environment and target animal were assessed in the previous variation application (EMEA/V/C/000136/II/0036), where the applicant submitted a Good Laboratory Practice (GLP)-compliant safety study, which demonstrated that repeated immunisation with Improva*c* is safe from eight weeks of age in gilts. Thus, the safety of Improvac immunisations of gilts from 10 weeks of age can be considered demonstrated and is not considered to impede the widening of the immunisation interval to eight weeks.

2.2. Efficacy

One new pivotal field study was submitted:

- "Assessment of efficacy of Improvac in gilts from 10 weeks of age under controlled field conditions in Belgium." (Report C826C-BE-20-052)

The field study was designed to confirm that two doses of Improvac, administered with an 8-week inter-dose interval, would be efficacious in gilts under field conditions, to provide more flexibility to the use as this is of practical importance in the pig industry, and support the already approved claim of Improvac in female pigs in the European Union.

The primary efficacy endpoint was the reproductive tract variables (weight of uterus, length of uterus horn, weight of ovaries and presence of follicles), and secondary efficacy variables were standing oestrus suppression, serum levels of anti-GnRF antibodies and the serum levels of the ovarian steroid hormones' progesterone and oestradiol. Since the applicant elaborated on the positive correlation between these reproductive tract variables and standing oestrus, the choice of the primary efficacy criteria is considered justified, instead of standing oestrus suppression as done in the previous variation application (variation EMEA/V/C/000136/II/036). The choice of the primary efficacy endpoint is relevant when considering the claim of Improvac as stated in the PI (suppression of oestrus, prevention of pregnancy).

The study was performed on a commercial Belgian farm according to Good clinical practice (GCP) principles. Study animals were randomly allocated to two treatment groups, using a generalized block design, of 40 crossbred (Crossbreed of a Piétrain boar and a hybrid sow) gilts in each group (80 gilts included in total). Animals enrolled in this study were approximately 10 weeks (64 to 71 days) old on day 0 (day of first treatment administration).

In study group T02 a dose of 2 ml Improvac was administered by the subcutaneous route on two occasions (10 and 18 weeks of age) which is in accordance with the intended administration scheme of the commercial product. The two vaccine batches used were commercial batches of Improvac. Two mL saline was used as a control product in study group T01. The pigs were slaughtered at an approximate age of 27 weeks (183-190 days old), i.e. 9 weeks after the second dose.

All study personnel conducting animal assessments were blinded. No animals were withdrawn during the study period. One pig from the T02 group was found dead at day 48 due to an intestinal torsion.

The study showed a statistically significant reduction of uterus weight, uterine horn length, ovarian weight and follicle size scores. In regard to follicle development the control group showed high scores for follicle development (all 67 scored ovaries showed some degree of development, i.e. categories 1, 2 or 3), whereas 51 of 53 scored ovaries in the Improvac group showed no signs of development ($P<0.0001$). It should be mentioned that the conclusion and the statistics are based on a limited amount of data since 51.3% of the animals from the T02 group (Improvac group) had some degree of missing reproductive tract when uterus (and uterine horns) and ovaries were returned from the slaughterhouse. The applicant explained that it is more likely that the reproductive tract was immature and small in Improvac treated animals increasing the probability of being missed or only partly removed by the slaughterhouse personnel, who was not aware of the study during slaughter. The strength of the presented amount of new data would have been considered stronger if the degree of lost material at the slaughterhouse were lower and the same between groups. However overall, when considering the 3R principles, the amount of data presented in the previous variation application and considering the presented justification regarding power calculations and estimation of sample sizes the CVMP agrees with the applicant and although a substantial amount of material was missing it is highly unlikely to have impacted the outcome. Evidence presented is sufficiently strong to demonstrate efficacy in the new proposed posology in females.

Standing oestrus was assessed on 23 study days, assessed from two weeks after the last administration and until the end of the study. This was done on study days 70, 74, 75, 76, 78, 81, 83, 85, 88, 90, 92, 95, 96, 97, 99, 102, 104, 106, 109, 111, 113, 116 and 118. Standing oestrus was observed at least once post last injection in 9 of 40 control animals (T01) versus 0 of 39 Improvac-treated gilts (T02) (P=0.0029). When standing oestrus was combined with swollen vulva as a new parameter "oestrus and/or swollen vulva", this was observed at least once post last injection in 17 of 40 control animals (T01) versus 0 of 39 Improvac-treated gilts (T02), P<0.0001). One gilt (Animal number 08) was clearly cycling from the Improvac treated group, although not showing standing oestrus and/or swollen vulva, but based on the findings of the reproductive tract of that gilt (820 g for uterus weight, 1555 mm mean horn length, with a total ovary weight of 20 g and presence of mature follicles and luteal tissue in both ovaries). Oestrus was not assessed for all the planned study days (approximately, this was not assessed as planned for 10% of total pig oestrus detection days) but this occurrence was similar in between T01 and T02.

Blood sampling was done on study days -1 and 55 with respectively 15,13,15,14 and 6 days intervals after day 55, being study day 70, 83, 98, 112 and 118.

Anti-GnRF antibodies were measured in serum from blood samples that were collected on study Days -1, 55, 70, 83, 98, 112 and 118. Antibody titer levels remained low in the control group, whereas a significant increase was seen in the immunised animals (T02) (P<0.0001) from day 55 and until the end of the study when compared to the control group.

Serum progesterone was detected from blood samples that were collected on study Days -1, 55, 70, 83, 98, 112 and 118. The level of progesterone detected in serum was significantly (P< 0.05) lower from day 98 until the end of the study for the vaccinated animals in treatment T02.

Oestradiol levels were measured in serum from blood samples that were collected on study Days -1, 55, 70, 83, 98, 112 and 118. Almost all the samples were below the level of quantification for oestradiol and there were no significant differences in oestradiol levels between treatment groups. The measuring of oestradiol was, as also seen in the data presented in the previous variation application, not showing a significant difference between T01 and T02. The applicant explained this lack of significant difference with the fact that oestradiol rises in peaks, in contrast to progesterone, and therefore may not be a good indicator for oestrus if the peak is not present on the chosen blood sampling days. The applicant chose to include oestradiol measurements anyway as a supportive "nice to have" parameter, although better results would most likely have been reported with a sufficient number of sampling days with more narrow sampling intervals. The applicant explained that the option to increase the number of sampling days was discarded for animal welfare reasons. Blood sampling animals at relevant narrow intervals (e.g. every two days for 6 weeks) would most likely have increased the stress of the animals to a significant extent and was not desirable. Nevertheless, the CVMP considers that the efficacy of Improvac has been demonstrated by the other variables analysed (reproductive tract variables, standing oestrus, anti-GnRF antibodies values, and progesterone values).

Overall conclusion on efficacy

The results demonstrated significant differences in the reproductive tract variables (weight of the uterus, uterus horn length, weight of the ovaries, and presence of follicles) 9 weeks after the second Improvac administration. In addition, the results of the laboratory analysis and the oestrus detection data analysis demonstrated that the administration of Improvac induced an anti-GnRF antibody response, decreased the levels of progesterone and suppressed standing oestrus. Almost all the samples were below the level of quantification for oestradiol and there were no significant differences in oestradiol levels between treatment groups.

The CVMP finds that the overall evidence to support the new posology in female pigs is demonstrated.

Variation G.I.18. To update the product information according to QRD template version 9.0

Comments regarding this variation have been also provided in the Product Information (PI).

3. Benefit-risk assessment of the proposed change

In female pigs, this product is authorised for the induction of antibodies against GnRF to produce a temporary immunological suppression of ovarian function (suppression of oestrus) in order to reduce the incidence of unwanted pregnancies in gilts intended for slaughter, and to reduce the associated sexual behaviour (standing oestrus). The onset of immunity (induction of anti-GnRF antibodies) can be expected within 1 week post second vaccination. Reduction of sexual behaviour (standing oestrus) can be expected from 1 to 2 weeks post second vaccination. The duration of immunological suppression of ovarian function has been demonstrated for 9 weeks after the second vaccination.

The proposed variation is to extend the inter-dose interval from 4 to 8 weeks, and to reduce the minimum age of vaccination accordingly (from 14 to 10 weeks of age) in female pigs and to update the product information according to QRD template version 9.0. The benefit of this variation is of practical importance in the pig production, thus being a more flexible inter-dose interval and the possibility of immunising gilts from 10 weeks of age instead of from 14 weeks of age.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of Improvac in gilts is to induce antibodies against GnRF to produce a temporary immunological suppression of ovarian function (ovarian suppression) resulting in prevention of unwanted pregnancies in gilts intended for slaughter, and to reduce the associated sexual behaviour (standing oestrus). No further direct therapeutic benefit is achieved for the animal from this variation application.

In relation to this variation application only one well-conducted pivotal field study (C826C-BE-20-052), in accordance with GCP, was submitted. This field study showed that when gilts were immunised at approximately 10 and 18 weeks of age, they demonstrated significant differences in the reproductive tract variables (weight of the uterus, uterus horn length, weight of the ovaries, and presence of follicles) 9 weeks after the second dose of Improvac was administered. Furthermore, and of most clinical importance, the study also demonstrated that this extended inter-dose interval from 4 to 8 weeks and the administration in younger gilts still induced an anti-GnRF antibody response, a decreased level of progesterone and suppressed standing oestrus, although one gilt in the Improvac treated group (T02 group) was clearly cycling though no standing oestrus was detected.

Although only one new study, at a single site and in a single breed was conducted, the presented evidence, when also considering the laboratory studies and field studies presented in the previous variation application (EMEA/V/C/000136/II/0036), which allowed the inclusion of the female claim in the Improvac SPC can be considered representative for the overall pig population. The presented results on efficacy, including the effect on anti-GnRF antibodies, the ability on reducing standing oestrus and the effect on the reproductive development demonstrate efficacy of Improvac when administered in females with the new more flexible posology, although a substantial amount of material was lost at the slaughterhouse but this is highly unlikely to have impacted the outcome. Evidence presented is

sufficiently strong to demonstrate efficacy with the new proposed posology in females, although one gilt in T02 entered into an oestrus cycle based on reproductive development data. In summary, the efficacy in gilts intended for slaughter in the overall conventional pig population was demonstrated. The applicant justified the choice of changing efficacy endpoints when compared to the previous variation application (EMEA/V/C/000136/II/0036) and a positive correlation between the two endpoints (primary and secondary) was demonstrated making the primary efficacy endpoint supportive of the claim of Improvac.

Additional benefits

The product has a wider and more flexible inter-dose interval when used in gilts and can be administered to gilts from 10 weeks of age (instead of from 14 weeks of age). Overall this is of practical importance in the pig production and therefore facilitates increased administration compliance in accordance with the SPC.

3.2. Risk assessment

Quality:

As no change have been introduced in the product manufacturing, quality remains unaffected by this variation and no concerns are to be addressed here.

Safety:

Safety remains unaffected by this variation as the risks for the user, consumer, environment and target animal were assessed in the previous variation application (EMEA/V/C/000136/II/0036), where the applicant submitted a Good Laboratory Practice (GLP)-compliant safety study, which demonstrated that repeated vaccinations with Improvac are safe from eight weeks of age in gilts. Thus, the safety of Improvac immunisations to gilts from 10 weeks of age is considered demonstrated and is not considered to impede the widening of the immunisation interval to eight weeks.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

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

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 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 (Regulation (EU). 2019/6), as follows:

To extend the inter-dose interval from 4 to 8 weeks, and to reduce the minimum age of vaccination accordingly (from 14 to 10 weeks of age) in female pigs (G.I.4) and to update the product information according to QRD template version 9.0 (G.I.18).

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

I, II, IIIA and IIIB

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

As a consequence of these variations, sections 2, 3.1, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.1, 5.5, 9 and 10 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.