Veterinary Medicines Directorate

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**NATIONAL PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Syvac Ery Parvo Emulsion for Injection for Pigs

**Date Created: December 2022**

# MODULE 1

## PRODUCT SUMMARY

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| Name, strength and pharmaceutical form | Syvac Ery Parvo Emulsion for Injection for Pigs |
| Applicant | Laboratorios SYVA S.A.<br>C/ Marqués de la Ensenada, 16<br>28004 Madrid<br>Spain |
| Active substance(s) | Inactivated *Erysipelothrix rhusiopathiae,* serotype 2, strain SE-9<br>Inactivated Porcine parvovirus, strain PVP-7 |
| ATC Vetcode | QI09AL01 |
| Target species | Pigs |
| Indication for use | For the active immunisation of gilts, sows and boars to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by Erysipelothrix rhusiopathiae, serotype 2, as shown under experimental challenge conditions in seronegative pigs.<br><br>For the active immunisation of gilts and sows for the reduction of transplacental infection in progeny caused by porcine parvovirus.<br><br>Onset of immunity:<br>E. rhusiopathiae: 3 weeks after completion of the primary vaccination scheme.<br>Porcine parvovirus: from the beginning of the gestation period.<br><br>Duration of immunity:<br>E. rhusiopathiae: 5 months<br>Porcine parvovirus: for the duration of gestation. |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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| Legal basis of original application | GB-National application in accordance with Article 12(3) of Directive 2001/82/EC as amended. |
| Date of conclusion of the procedure | 23/09/2022 |

## I. SCIENTIFIC OVERVIEW

Syvac Ery Parvo Emulsion for injection for pigs is a bivalent inactivated adjuvanted vaccine for intramuscular injection in pigs to reduce clinical signs of swine erysipelas and in female pigs for the protection of progeny against transplacental infection caused by porcine parvovirus. The active substances in the formulation are inactivated *Erysipelothrix rhusiopathiae*, strain SE-9 of serotype 2, and inactivated porcine parvovirus, strain PVP-7. The vaccine is adjuvanted with Montanide ISA 201 VG and contains thiomersal as a preservative.

The proposed primary vaccination schedule is two 2 ml intramuscular doses, 4 weeks apart, from 5 months of age and 2-3 weeks before mating. Revaccination using a single 2ml dose is recommended prior to subsequent mating.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1]
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### *II.A. Composition*

Each 2 ml dose contains:

**Active substance:**
Inactivated *Erysipelothrix rhusiopathiae*, serotype 2, strain SE-9 7.4 – 61.0 ELISA Units*

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

Inactivated Porcine parvovirus, strain PVP-7320 – 5120 HIT**
* Serological response in vaccinated mice determined by ELISA according to Ph. Eur. 0064
** Titre of antibodies determined in vaccinated guinea by haemagglutination inhibition test according to Ph. Eur. 0965

**Adjuvants:**
Montanide ISA 201 VG 0.91 g

**Excipient:**
Thiomersal 0.2 mg

The other excipients are Potassium chloride, Potassium dihydrogen phosphate, Disodium phosphate, Sodium chloride, Silicone antifoaming agent and water for injections.

The container/closure system consists of a polypropylene flask closed with a bromo-butyl rubber stopper and an aluminium cap. Flasks (50ml or 100ml) are inserted into a cardboard box with the package insert. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant (Montanide ISA 201 VG), the vaccine strains (*Erysipelothrix rhusiopathiae* strain SE-9 and porcine parvovirus strain PVP-7) and presence of preservative (thiomersal) are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

## *II.B. Method of Preparation of the Product*

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of preparing the two antigens separately and then combining into the finished product. The two prepared antigens and thiomersal solution are added to a mixing reactor with the other excipients following sterilisation to create an aqueous fraction. The aqueous fraction is then added to a mixing reactor with the adjuvant to form an emulsion. The emulsion is then maintained in the reactor for up to three days prior to filling, packaging and then release.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

## *II.C. Control of Starting Materials*

The active substances are established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

Most starting materials of non-biological origin used in production comply with European pharmacopoeia monographs. There are some other non-biological

starting materials not listed in a pharmacopoeia, the use of these have been justified.

Some biological starting materials used (Bovine serum and Gelatin) are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents.

Other starting materials of biological origin are not described in a pharmacopeia, these include the following: *Erysipelothrix rhusiopathiae*, serotype 2, strain SE-9, Porcine parvovirus, strain PVP-7, MPK cell line, Casein meat peptone (polypeptone peptone), Lactalbumin enzymatic hydrolysate and Trypsin- EDTA solution. The use of these have been individually justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

### *II.C.4. Substances of Biological Origin*

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

## *II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process*

The tests performed during production are described and the results of four consecutive runs, conforming to the specifications, are provided.

## *II.E. Control Tests on the Finished Product*

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include appearance, identification of both active substance, sterility, potency of both active substances, viscosity, density, stability of the emulsion, content of thiomersal, residual formaldehyde, pH, filling volume and secondary packaging. The tests carried out comply with the requirements of the specific Ph. Eur. monographs (Swine erysipelas vaccine inactivated – 0064 and Porcine parvovirosis vaccine inactivated – 0965).

The demonstration of the batch-to-batch consistency is based on the results of five batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

## *II.F. Stability*

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The in-use shelf-life after first opening the immediate packaging (10 hours) is supported by the data provided.

### *G. Other Information*

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

This shelf life was proposed based on stability data covering storage of the vaccine in filled vials for 27 months at 2-8ºC.

## III. SAFETY ASSESSMENT

Potential adverse effects derived from administration of the vaccine on target species have been determined through three safety laboratory studies, two efficacy laboratory studies, and two field studies.

The three safety laboratory studies and the safety field study were done with batches of Syvac Ery Parvo at the maximum potency. One efficacy laboratory study was done with different batches prepared at maximum, standard, minimum and subpotent potency. The other efficacy laboratory study was done with a batch at minimum potency. The clinical trials were done with a maximum potency and a standard batch of the vaccine, respectively.

### *Laboratory trials*

A single safety study was carried out to fulfil requirements for the safety of the administration of one dose and safety of the repeated administration of one dose. Therefore, a specific one dose safety study was not performed. There is no requirement for overdose studies as the proposed vaccine is inactivated. To meet the specific requirement of Ph. Eur. monograph 0965 section 2-3-1-1-3, results of safety in pigs used in the test for immunogenicity in two efficacy laboratories studies were also provided.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The corresponding Ph.Eur. monographs were followed (0064 and 0965).

Effects on reproductive performance were examined and the conclusions adequately reflected on the SPC.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used are montanide (no MRL required), thiomersal (MRL not applicable), silicone antifoam and PBS. Based on the provided information, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

### *Field studies*

Two field studies were carried out intended to support the safety of administration of the product during pregnancy:

A field study was performed in sows/gilts to demonstrate the safety and efficacy of the intramuscular administration of Ery/Parvo compared to a positive control vaccine.

A second safety field study was carried out in pregnant gilts and sows and lactating sows that had been vaccinated against swine erysipelas and porcine parvovirus in previous reproductive cycles. The aim of this study was to obtain additional data in seropositive sows to complete the examination of the reproductive performance carried out under laboratory conditions.

The results supported the safety use of the vaccine in all the studied categories.

### *Ecotoxicity*

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is not expected to pose a risk for the environment when used according to the SPC. This was based on that the vaccine is an inactivated vaccine and does not contain infectious biological particles. The vaccine is intended to be administered by intramuscular injection, which directly avoids direct or indirect contact of the vaccine to the environment. However, in the case of accidental spillage a risk is identified and the proposed SPC includes a warning in mitigation of the identified risks.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

## IV. CLINICAL ASSESSMENT (EFFICACY)

### *Clinical Studies*

### *Laboratory Trials*

The applicant has conducted six laboratory trials and one field study to demonstrate the efficacy of the candidate vaccine.

These studies were in accordance with the relevant requirements, which show that the vaccine produces an active immunisation in gilts, sows and boars to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 2. Additionally, the vaccine produces an active immunisation of gilts and sows for the reduction of transplacental infection in progeny caused by porcine parvovirus.

Laboratory studies testing the vaccine against swine erysipelas

As an initial step to investigate the efficacy of the vaccine, the challenge model proposed by Paul-Erlich-Institute (Johannes *et al*., 1998; Cussler *et al*. 2001) and described in the *Ph. Eur. 0064* was evaluated.

Once the challenge model was established, two laboratory studies involving vaccination and challenge were conducted to demonstrate evidence of the efficacy of the product with the proposed vaccination schedule:

- One of the studies was designed to study the onset of immunity after completion of the primary vaccination schedule. This study also investigated the effective dose by using four different formulations of the vaccine with different antigenic payloads.
- A second study focused on the duration of immunity, showed to be 5-months after primary vaccination. Subsequently, efficacy of revaccination with a single dose was demonstrated by challenge of the animals 5 months later (phase two of this second study).

Laboratory studies testing the vaccine against porcine parvovirus (PPV)

The first laboratory study performed focused on validating the challenge. The objective was to reproduce a standard PPV infection model to be used in the efficacy/immunogenicity test for PPV. The inoculum P2MPK was assessed in a challenge study according to *Ph. Eur. 0965*.

Once the challenge model was validated, the following studies were performed to assess the efficacy of the vaccine against PPV with the proposed vaccination schedule:

- The first one assessed the efficacy of the vaccine and the effective dose, using four different formulations of the vaccine with different antigenic potencies.

- The second study assessed the efficacy of the revaccination of a single dose administered after the completion of the primary vaccination schedule.

Efficacy of the vaccine against swine erysipelas

Efficacy of vaccination was demonstrated in controlled laboratory challenge studies by intradermal administration of *E. rhusiopathiae*, serotype 2, strain NF4. At challenge, 21 days after vaccination, 7 of 7 (100%) of unvaccinated control animals were confirmed as diseased. Vaccinated animals (with the standard potency batch) showed no signs of the disease (skin lesions) (12 of 12 animals (100%)).

The duration of protection was tested in a second study and established in 5 months. In this study, twelve vaccinated pigs and 7 control pigs were submitted to challenge five months after primary vaccination or saline solution administration, for vaccinated and control groups, respectively. The challenge was done by intradermally administration of *E. rhusiopathiae*, serotype 2, strain NF4. In pigs from the control group, generalized skin lesions were

observed in all animals (7 of 7 animals (100%). In the vaccinated group, one out of 12 animals (8.33%) showed skin lesions of moderate size.

The duration of revaccination was also assessed. Twelve vaccinated animals were treated with a third dose of the vaccine five months after primary vaccination. As a control group, 7 animals were administered three doses of saline solution following the same vaccination scheme as in the treated animals. These subgroups were challenged 5 months after the third dose administration. In the control group, the 7 pigs developed typical skin lesions from day 1 or day 2 post-challenge. Lesions generalized in all animals at day 5 post-challenge. In the vaccinated group, 1 out of 12 animals (8.33 %) developed diamond-shaped skin lesions that appeared at day 4 post-challenge.

*Summary table of the efficacy studies of the vaccine against swine erysipelas*

| **Animals Groups Number Age** | **Antibody status** | **Vaccine: route of administration** | **Challenge: Day post-vaccination** | **Follow up: Duration Endpoints*** | **Results: Cases/total (%) (for standard antigen content batch)** | | **% Efficacy (95% CI)**** |
|---|---|---|---|---|---|---|---|
| **Study 1** | | | | | Vaccinates | Controls | |
| Onset of immunity:<br><br>Pigs<br>12 weeks old<br><br>Vaccinates:<br>12 pigs per group<br><br>Controls: 7 pigs | Negative | Group 1: vaccine at 4 times the standard antigen content.<br><br>Group 2: standard antigen content.<br><br>Group 3: substandard potency vaccine.<br><br>Group 4: highly substandard potency vaccine.<br><br>Control group: placebo (saline) | 21 days | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>Endpoint 2: Antibodies against Erysipelas<br><br>Endpoint 3: Rectal temperature<br><br>Endpoint 4: General signs | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>0/12 (0%) | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>7/7 (100%) | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>100% |
| **Study 2** | | | | | Vaccinates | Controls | |
| Duration of immunity (DOI): | Negative | Standard antigen content. | <u>Subgroup 1 (DOI after primary vaccination):</u> | Endpoint 1: Clinical signs of the disease caused by | <u>Subgroup 1 (DOI after primary vaccination):</u> | <u>Subgroup 1 (DOI after primary vaccination):</u> | <u>Subgroup 1 (DOI after primary vaccination):</u> |

| **Animals Groups Number Age** | **Antibody status** | **Vaccine: route of administration** | **Challenge: Day post-vaccination** | **Follow up: Duration Endpoints*** | **Results: Cases/total (%) (for standard antigen content batch)** | | **% Efficacy (95% CI)**** |
|---|---|---|---|---|---|---|---|
| Subgroup 1 (DOI after primary vaccination):<br>Pigs<br>12 weeks old<br>Vaccinates:12<br>Controls: 7<br><br>Subgroup 2 (DOI after revaccination administered 5 months after primary vaccination):<br>Pigs<br>12 weeks old<br>Vaccinates:12<br>Controls: 7 | | Saline solution. | 152 days (5 months)<br><br>Subgroup 2 (DOI after revaccination administered 5 months after primary vaccination):<br>150 days (5 months) | Erysipelas<br><br>Endpoint 2: Antibodies against Erysipelas<br><br>Endpoint 3: Rectal temperature<br><br>Endpoint 4: General signs | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>1/12 (8.33%)<br><br>Subgroup 2 (DOI after revaccination administered 5 months after revaccination):<br><br>Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>1/12 (8.33%) | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>7/7 (100%)<br><br>Subgroup 2 (DOI after revaccination administered 5 months after revaccination):<br><br>Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>7/7 (100%) | Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>91.6%<br><br>Subgroup 2 (DOI after revaccination administered 5 months after revaccination):<br><br>Endpoint 1: Clinical signs of the disease caused by Erysipelas<br><br>91.6% |

*Specified according to efficacy endpoints relating to claims in the indication. Primarily, primary endpoints should be listed but secondary endpoints relevant for the indications can be included

** Vaccine efficacy = $\frac{\text{cases}_{\text{controls}}/\text{total}_{\text{controls}} - \text{cases}_{\text{vaccinates}}/\text{total}_{\text{vaccinates}}}{\text{cases}_{\text{controls}}/\text{total}_{\text{controls}}} \times 100$

Efficacy of the vaccine against porcine parvovirus

The efficacy of the vaccine against porcine parvovirus was demonstrated in controlled laboratory challenged studies.
The challenge strain was validated in a separate study. The selected strain was PPV strain NADL-8.
The following studies were performed to assess the efficacy of the vaccine against porcine parvovirus:

- The first study was designed to assess the efficacy of the vaccine using four different formulations of the vaccine with different antigenic potencies (high, standard, and two sub-standard antigen potencies). Each group was vaccinated with one of the batches of the vaccine. In addition, a control group was also included and inoculated with placebo.
The gilts were vaccinated according to the proposed vaccination scheme consisting of two injections of 2 ml each separated by an interval of 4 weeks. The second dose was administered 2-3 weeks before mating.
The artificial insemination occurred on 2 consecutive days on the first oestrus. Pregnancy was confirmed by ultrasounds around 20 days after insemination and non-pregnant gilts were withdrawal from the study.
At the 40$^{th}$ day of gestation, gilts were challenged and subsequently euthanized at about the 90$^{th}$ days of gestation. The foetuses were examined for infection with PPV. Protection was assessed by confirming absence of PPV.
Safety of the vaccine was also evaluated by monitoring rectal temperature and local and systemic reactions after each vaccination.

-The second study assessed the efficacy of the revaccination of a single dose administered after the completion of the primary vaccination schedule. This study was performed as a controlled and blinded study using 27 sows distributed in two groups.
Animals enrolled in the study were gilts of 5 months of age, free of antibodies against PPV and in good health conditions.
One group was vaccinated with Syvac Ery Parvo vaccine and the other group was inoculated with a placebo.
The vaccine used was formulated to obtain a sub-standard potency vaccine.
Gilts were vaccinated according to the proposed primary vaccination scheme consisting of two injections of 2 ml each separated by an interval of 4 weeks. The second dose was administered 2-3 weeks before mating.
After artificial insemination, animals were subjected to a pregnancy diagnosis. The pregnant animals were maintained under observation during the reproductive cycle and revaccinated at lactation, 2-3 weeks before the second mating, with a single dose of 2 ml.
Pregnancy was confirmed by ultrasounds prior to challenge. At the 40$^{th}$ day of the second gestation, sows were challenged and subsequently euthanised at about the 90$^{th}$ day of gestation and their foetuses were examined. Infection of the foetuses by PPV was assessed.
Safety of the vaccine was also evaluated by monitoring rectal temperature and local and systemic reactions after each vaccination.

*Summary table of the efficacy studies of the vaccine against porcine parvovirus*

| **Animals Groups Number Age** | **Antibody status** | **Vaccine: route of administration** | **Challenge: Day post-vaccination** | **Follow up: Duration Endpoints*** | **Results: Cases/total (%) (for standard antigen content batch)** | | **% Efficacy** |
|---|---|---|---|---|---|---|---|
| **Study 1** | | | | | Vaccinates | Controls | |
| Onset of immunity:<br><br>Gilts (5-6 months of age)<br>Vaccinates:12/group<br>Controls: 9 | Negative | Group 1: vaccine at 4 times the standard antigen content<br><br>Group 2: standard antigen content.<br><br>Group 3: substandard potency vaccine<br><br>Group 4: highly substandard potency vaccine<br><br>Control group: placebo (saline) | 40th days of gestation | Endpoint 1: Infection of the foetuses<br><br>Endpoint 2: Antibodies against PPV in gilts<br><br>Endpoint 3: Abortion and general clinical signs | Endpoint 1: Infection of the foetuses (standard batch)<br><br>4/115 (3.5%) | Endpoint 1: Infection of the foetuses<br><br>67/67 (100%) | Endpoint 1: Infection of the foetuses<br><br>96.5% |
| **Study 2** | | | | | Vaccinates | Controls | |
| Duration of immunity (DOI): | Negative | Vaccine: Sub- | 40th days of gestation after | Endpoint 1: Infection of | Endpoint 1: Infection of the | Endpoint 1: Infection of the | Endpoint 1: Infection of the |

| **Animals Groups Number Age** | **Antibody status** | **Vaccine: route of administration** | **Challenge: Day post-vaccination** | **Follow up: Duration Endpoints*** | **Results: Cases/total (%) (for standard antigen content batch)** | | **% Efficacy** |
|---|---|---|---|---|---|---|---|
| Gilts (5-6 months of age)<br>Vaccinates:16/group<br>Controls: 11 | | Standard antigen content.<br><br>Saline solution | primary vaccination (2 doses) and revaccination (1 dose) | the foetuses<br><br>Endpoint 2: Antibodies against PPV in gilts<br><br>Endpoint 3: Abortion and general clinical signs | foetuses (sub standard batch)<br><br>4/156 (2.7%) | foetuses<br><br>87/92 (94.6%) | foetuses<br><br>97.4% |

*Specified according to efficacy endpoints relating to claims in the indication. Primarily, primary endpoints should be listed but secondary endpoints relevant for the indications can be included.

** Vaccine efficacy = $\frac{\text{cases}_{\text{controls}}/\text{total}_{\text{controls}} - \text{cases}_{\text{vaccinates}}/\text{total}_{\text{vaccinates}}}{\text{cases}_{\text{controls}}/\text{total}_{\text{controls}}} \times 100$

### *Field Trials*

One field study was conducted which is intended to support efficacy results derived from laboratory trials.

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| Study title | "Field study to test the safety and efficacy in breeding sows/gilts of an inactivated vaccine against *E. rhusiopathiae* and Porcine Parvovirus"<br>Code T&T - SYV-14-004_PPV-MR |
| Objectives | To evaluate the safety and efficacy of the vaccine in gilts and sows from 6 months of age under commercial conditions. The study was designed as a positive controlled, randomised and blinded study. |
| Test site(s) | The study was a multisite clinical study performed by the CRO Test &Trials S.L. (Monzón, Huesca, Spain). |
| Compliance with Regulatory guidelines | In accordance with the principles of Good Clinical Practice (GCP) |
| Test Product | A standard batch of the test vaccine was used to perform the clinical trial. The batch (190112S) was manufactured as an industrial batch following the defined methodology for the manufacture of the vaccine.<br><br>2 ml dose<br>*E. rhusiopathiae* serotype 2, 4 mg (dry weight)/ Potency 12.5 ELISA U<br>PPV $10^{8.0}$ $CCID_{50}$/ 2560 *HIA<br>Montanide ISA ™ 201 VG 0.91 g<br>Thiomersal 0.20 mg<br>PBS q.s.f 2 ml<br><br>*HIA: Titre of antibodies determined by inhibition of haemagglutination |
| Control product/placebo | An authorised product, Eryseng Parvo, (Product number: EU/2/14/166/001-007, Marketing Authorisation Holder: Laboratorios Hipra) was used as the positive control.<br><br>2 ml dose<br>*E. rhusiopathiae*, strain R32E11 > 3.34 $log_2$ *$EI_{50\%}$<br>PPV, strain NADL-2 **RP > 1.15<br>Aluminium hydroxide 5.29 mg (Aluminium)<br>Ginseng<br>DEAE-Dextran<br><br>* EI50% refers to ELISA Inhibition 50%<br>**RP refers to relative potency (ELISA) |
| Animals | A total of 648 animals were included in the study. 342 gilts healthy and unvaccinated against erysipelas and |

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| | PPV from 6 months of age were included in the 1st phase and 306 primiparous and multiparous breeding sows vaccinated against erysipelas and PPV with any authorised vaccine in the previous reproductive cycle, were included in 2nd phase of the study. |
| Randomisation | Randomised. |
| Blinding | Blinded |
| Method | Vaccine and positive control were administered in parallel, following identical procedures. Products were injected in the neck of the animals as follows:<br>First administration: D0 of the study, 2 ml, right side.<br>Second administration: D28 of the study, 2 ml, left side.<br>The third dose was applied in the right side on D177.<br><br>The 342 gilts were divided into two groups (171 per group) and vaccinated with the test vaccine or a positive authorised Control Product (CP) according to the primary vaccination scheme proposed (D0: 1st dose and D28 2nd dose i.e. 2 weeks before mating).<br><br>The 306 breeding sows were also divided into two groups (153 per group) and revaccinated with a single dose of the test vaccine or CP on D28 of the study (3 weeks before mating).<br><br>The efficacy evaluation consisted of the assessment of reproductive parameters for PPV as well as the presence of clinical signs and mortality associated to erysipelas. In addition, blood collection was carried out monthly to investigate the antibody titres against erysipelas and PPV in a representative number of animals.<br><br>The following were evaluated after vaccination as efficacy parameters:<br><br>For PPV:<br>• Conception rate (return to service). Abortion rate.<br>• Reproductive performance at farrowing (live and healthy piglets, weak, stillborn and crushed/dead) and at weaning (proportion of weaned piglets per litter).<br>• Serology against PPV performed in 20 gilts and 20 primiparous and multiparous sows per group and site.<br><br>For erysipelas:<br>• The frequency of deaths caused by erysipelas (spleen samples taken for isolation of the pathogen in case of compatible or suspicious clinical signs).<br>• Serology against erysipelas performed in 20 gilts |

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| | and 20 primiparous and multiparous sows per group and site. |
| Statistical method | The number of animals included in the study was calculated to allow the detection of 1.5 % difference between treatment groups in the number of mummified piglets with 80 % potency and 95 % confidence level. The minimum sample size was 118 animals per group however more animals were included to prevent possible losses during the study.<br><br>Each sow/gilt was the experimental unit for statistical purposes. Each litter was the experimental unit for the assessment of the reproductive performances. All data were imported into Rv. 4.0.3 for management and evaluation. Descriptive statistics or frequency tables were generated for all variables that were statistically evaluated. Sample size was calculated to have 80% power to detect a difference of 1.5 % of mummified foetuses between treatment groups assuming that the common standard deviation is 4 using the Wilcoxon Mann-Whitney test with a 0.05 two-sided significance level α. Proportions were compared by Fisher´s exact test or Wilcoxon Mann-Whitney test. Antibody titres were compared by analysis of variance. Level of significance used in all cases was $p \leq 0.05$. |
| RESULTS | |
| Participant flow | A total of 111 animals (60 from test vaccine Group and 51 from CP Group) were excluded from the study during Phase 1 whereas 49 animals (29 from IPV Group and 20 from CP Group) were excluded during Phase 2. The applicant reports that the main causes of exclusion were musculoskeletal and reproductive disorders that were not attributable to the vaccine or PPV or erysipelas infections. Statistical analysis confirmed that there was no significant difference in the proportion of excluded animals between groups. In addition, there were a number of lost to follow up animals in both phases, 49 animals in Phase 1 (19 from test vaccine Group and 15 from CP group) and 7 animals in Phase 2 (1 from test vaccine Group and 6 from CP Group). |
| Outcomes for endpoints | **Circulation of wild-type PPV strains**<br>Presence of the PPV virus was confirmed in the 3 farms either by PCR or serology. From 10 to 23 % of the samples from each farm tested positive to PCR and 64 to 87 % of serology samples were positive in each farm.<br><br>**Presence of disease caused by *E. rhusiopathiae***<br>Symptoms and/or lesions attributable to erysipelas were not found in any animal from the 3 farms during the |

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| | study. Additionally, samples collected from corpses presented PCR negative results to erysipelas.<br><br>**Efficacy against PPV:**<br>Proportion of mummified piglets<br>The number of mummified piglets was considered the primary parameter to evaluate the efficacy of the test vaccine. This amount in the IVP Group (3.52 %) was not significantly higher than in the CP Group (3.11 %). Non-inferiority test results for efficacy were shown ($p < 0.05$). All mummified piglets found in both groups were negative to PPV by PCR, as well as the stillborn piglets analysed.<br>Conception rate (return to service) and abortion rate<br>The number of sows returning to service were lower than 7 % and 1 % in Phase 1 and Phase 2 respectively in both CP and test vaccines. No statistically significant difference between groups was found ($p > 0.05$).<br><br>PPV serology<br>34 % of the total gilts enrolled, were seropositive to PPV at the beginning of the study. Antibody titres increased significantly after primary vaccination of gilts or revaccination of primiparous and multiparous sows in both groups in Phase 1, followed by a slight decrease up to D147. No statistically significant difference was observed between test vaccine and CP.<br><br>In Phase 2, revaccination of former gilts also produced a significant increase in the antibody titres. The level of antibodies was thereafter maintained until the end of the study. As for Phase 1, no statistically significant difference was observed between test vaccine and CP<br><br>**Efficacy against *E. rhusiopathiae:***<br>Number and proportion of animals with rhomboidal erythema skin lesion<br>No rhomboidal erythema skin lesion was observed during the study in any of the animals.<br><br>Number and proportion of deaths caused by *E. rhusiopathiae*<br>None of the animals that died during the study presented symptoms of erysipelas. In addition, the samples collected from the dead animals were negative to PCR.<br><br>Erysipelas serology<br>All the gilts enrolled were seronegative to *E. rhusiopathiae* at the beginning of the study, apart from 2 animals included in the control group. Seroconversion was observed after vaccination as most of the gilts were seropositive on D37 and all of them on |

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| | D69. Significant difference ($p > 0.05$) between groups in the proportion of seropositive animals was only detected on D147 of the study in favour of the IVP Group (91.94 % vs 74.55%). Maximum titres were reached on D69, decreasing in both groups thereafter. Revaccination with the third dose, boosted antibody titres. No difference was observed between the two groups on antibody titres during the study.<br>Most of the primiparous and multiparous sows vaccinated in Phase 1 presented antibodies against *E. rhusiopathiae* at the beginning of the Phase 2 of the study (less than 18 % were seronegative in both groups). All the animals presented antibodies on D37 after vaccination. Maximum titres were reached on D37, decreasing in both groups thereafter. There was no significant difference in the proportion of seropositive animals or in titres between groups. |
| Conclusions | In conclusion, this field trial showed a non-dissimilar efficacy of the test vaccine, in comparison to positive control group against PPV when used following the proposed primary schedule and / or as revaccination in gilts and (previously vaccinated) sows.<br><br>The following conclusions were obtained after administration of Syvac Ery/Parvo to animals from 6-month-old under field conditions compared with a positive control:<br>• No records of dead or abortion attributable to the vaccine were recorded in this study<br>• Non-inferiority on the proportion of the mummies at farrowing was observed in Syvac Ery/Parvo group compared to the vaccine control group in three farms with active PPV circulation.<br>• Efficacy of the vaccine against erysipelas has not been proved in this trial due to the lack of evidence of circulation of agent in the farms. However, a seroconversion in unvaccinated gilts and an increase in the antibody titres in vaccinated sows were observed after administration of Syvac Ery/Parvo, responses comparable or higher to the one obtained with the positive control vaccine. |

## V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product is favourable.

# MODULE 4

## POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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