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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Suvaxyn PRRS MLV (EMEA/V/C/004276/VRA/0006/G)

Vaccine common name: Porcine respiratory and reproductive syndrome virus vaccine (live)

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

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Introduction

Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Zoetis Belgium (the applicant), submitted to the European Medicines Agency (the Agency) on 31 March 2022 an application for a group of variations requiring assessment for Suvaxyn PRRS MLV.

Scope of the variation

Suvaxyn PRRS MLV is already authorised for intramuscular use in pigs for active immunisation of clinically healthy pigs from 1 day of age in a porcine respiratory and reproductive syndrome (PRRS) virus-contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1). Suvaxyn PRRS MLV lyophilisate and solvent for suspension for injection for pigs contains $10^{2.2}$ – $10^{5.2}$ $CCID_{50}$ of modified live PRRSV, strain 96V198, and is presented in packs containing one glass vial of 15 ml of lyophilisate (25, 50 or 125 doses) and one HDPE vial of 50, 100 or 250 ml of solvent.

Variation(s) requested	
I.II.1.e	Changes to strength, pharmaceutical form and route of administration - Change or addition of a new route of administration
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

This variation is to add nasal use as an additional route of administration and to modify the approved therapeutic indication to include protection against heterologous subtype-1 AUT15-33, subtype-2 BOR57 and subtype-3 Lena strains of the PRRS virus.

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

Scientific advice

Not applicable.

Limited market status

Not applicable.

Part 1 - Administrative particulars

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements. The signed statement from the MAH and the QPPV that the QPPV has the necessary means to fulfil the tasks and responsibilities requested by Regulation (EU) 2019/6 has been provided.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

Cross-reference is made in the expert review to data already submitted and assessed by the CVMP during the marketing authorisation procedure of Suvaxyn PRRS MLV in 2017.

Study **C/394/13** "Onset of immunity of EU PRRS MLV in seronegative and seropositive 1-day-old pigs" evaluated the onset of immunity and assessed the efficacy of Suvaxyn PRRS MLV in the presence of maternally derived antibodies (MDA) after administration to seronegative and seropositive 1-day old pigs by intramuscular (IM) and intranasal (IN) route. Piglets were derived either from seronegative sows or from seropositive sows. At 1 day of age, animals were vaccinated with a dose 2.0 $\log_{10}$ $CCID_{50}$ at a volume of 2 ml either intramuscularly or intranasally with Suvaxyn PRRS MLV (lot VMRD13-015). Four weeks (d26 to d28) after vaccination, piglets were challenged with EU PRRSV isolate Olot/91 strain (batch No 021012) by IN route of 1 ml with a titre of 10^5 $TCID_{50}$/ml. Results of this study revealed that IN immunisation of seropositive 1-day old piglets was not efficacious against a respiratory challenge with EU PRRSV-1 Olot/91. The study was considered not valid, as no viraemia was observed in control piglets and levels of MDAs at challenge were too high to evaluate the effect of vaccination.

Studies **B824R-ES-14-437** "Duration of Immunity of the EU PRRS MLV administered to 1-day-old piglets against challenge with a European PRRSV isolate at approximately 18 weeks post-vaccination" and **B824R-ES-14-438** "Duration of Immunity of the EU PRRS MLV administered to 1-day-old piglets against challenge with an European PRRSV isolate at approximately 26 weeks post-vaccination" evaluated the duration of immunity (DOI) in seronegative respectively seropositive 1-day-old piglets. Animals were challenged 126 days (16 weeks) and 182 days (26 weeks) post-vaccination with EU PRRSV-1 isolate Olot/91. Results revealed that vaccinations were efficacious in reducing viraemia, nasal and oral shedding and reduced lung lesions after challenge infection.

Study **B828R-ES-14-341** "Assessment of the potential effect of maternally-derived antibodies on the efficacy of the Modified Live EU PRRSV Vaccine administered to 1-day-old seropositive pigs against challenge with a European PRRSV isolate" evaluated the influence of MDAs on the efficacy of a single dose of 2 ml with approximately $10^{2.5}$ $TCID_{50}$ Suvaxyn PRRS MLV (lot VMRD13-015) administered to seropositive 1-day old piglets either intramuscularly or intranasally. Intranasal challenge infection with EU PRRSV isolate Olot/91 (Passage 7, lot 180914, $10^{5.0}$ $CCID_{50}$ per animal, re-titrated $10^{4.3}$ $CCID_{50}$) with 2 ml intranasal (1.0 ml in each nostril) was applied 67 days after vaccination, when serum-neutralising (SN) titres were undetectable in control piglets. Results of this study could not demonstrate efficacy in seropositive 1-day old piglets by IN immunisation with Suvaxyn PRRS MLV.

The following **new studies** have been submitted:

Study reference	Study type	Age of piglets (days)	Vaccine dose ($CCID_{50}$/dose)	Challenge strain PRRSV-1
Evaluation of the efficacy of the intranasal administration route				
B825R-ES-20-983	OOI	3 to 4	2.2 log_{10}	subtype-1 Olot/91
B825R-ES-20-A59	MDA	2 to 3	2.2 log_{10}	subtype-1 Olot/91
Evaluation of protection against heterologous PRRSV-1 subtypes				
B825R-AT-17-714	OOI	1	2.2. log_{10}	subtype-1 AUT15-33
B825R-GB-17-715	OOI	1	2.2. log_{10}	subtype-2 BOR57/1
B825R-ES-17-716	OOI	1	2.2 log_{10}	subtype-3 Lena

Only these new data have been assessed in the sections below.

General requirements

Suvaxyn PRRS MLV, a porcine reproductive and respiratory syndrome virus (PRRSV) modified live vaccine, is intended for the intramuscular use in pigs for fattening from 1 day of age, gilts and sows. The vaccine is intended for the active immunisation of clinically healthy pigs from 1 day of age in PRRSV-contaminated environment to reduce viraemia and nasal shedding.

In fattening pigs, the claim to reduce lung lesions after challenge infection applied 26 weeks after vaccination is included. For seronegative 2-week-old piglets, additionally reduction of oral shedding is claimed.

The onset of immunity is 21 days, and the duration of immunity is 26 weeks after vaccination.

Efficacy studies were performed in compliance with the Regulation (EU) 2019/6, and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7.

Challenge model

For the **evaluation of the efficacy of the intranasal administration route** the **PRRSV-1 subtype-1 Olot/91 strain** was used. This strain has been already used and established in studies provided with the original documentation for the marketing authorisation of Suvaxyn PRRS MLV in 2017. Briefly, the original virus strain has been isolated in Spain in 1991 from a case of late-term abortion in sows. Material from lungs of stillborn piglets was grown on PAM (pulmonary alveolar macrophages) and passaged 4 times. This virus was designated as PRRSV isolate Olot/91 and analysed by ultra-deep next generation sequencing (Gene Bank acc. No. KF2031323). The challenge material was sterile filtrated, tested for PPV, PCV and *M. hyopneumoniae* by PCR, aliquoted and kept at -80±10 °C until use. The challenge virus was adjusted to a target titre of $10^{5.0}$-$10^{6.0}$ $CCID_{50}$/ml for IN administration.

For the **evaluation of protection against heterologous PRRSV-1 subtypes** three different challenge strains were used, and information was included in the dossier.

PRRSV-1 subtype-1 AUT15-33 challenge strain has been isolated form an outbreak in Austria in 2015. The challenge model has been developed at University of Vienna in Austria, with a challenge dose of $6.8x10^3$ $CCID_{50}$ per animal applied intranasally. Furthermore, it is highlighted that this challenge model has been already previously used to evaluate the efficacy of a vaccine of another company. AUT15-33 strain is originated from Austria with the GenBank acc. No KU494019 and further information on the establishment of the AUT15-33 challenge model has been provided. The target titre that was applied intranasally was $5x10^4$ $CCID_{50}$/ml ($1x10^5$ $CCID_{50}$/dose, back-titrated with $3.4x10^3$ $CCID_{50}$/ml and a total dose of $6.8x10^3$ $CCID_{50}$/dose).

PRRSV-1 subtype-2 BOR57 has been isolated in Belarus in 2004 and the challenge model was established at Moredun Scientific in the UK with a dose of $2x10^6$ $TCID_{50}$/ml by the IN route in 7-week-old piglets. After infection, the animals showed a rectal temperature increase post challenge (day 5 – 13) and lung lesions after 14 days of infection. Further information on the challenge model, including the lot number, the passage level, the origin (Hungary) and the validation of the model by Moredun Scientific and by publications has been provided. A target titre for challenge infection of approximately $1x10^6$ $TCID_{50}$/ml (back-titrated with $1.12x10^6$ $TCID_{50}$/ml) was applied intranasally into the left nostril of piglets with a volume of 5 ml (total dose of approximately $5x10^6$ $TCID_{50}$).

PRRSV-1 subtype-3 Lena strain was isolated in an outbreak in Belarus in 2007. The isolate was received from the University of Ghent, Belgium, and passaged in porcine alveolar macrophages (PAM) for the challenge stock preparation. The challenge stock was used to develop the challenge model in study **B821R-ES-17-757** with a challenge dose of $10^{2.5}$ or $10^{3.5}$ $TCID_{50}$ and the optimal necropsy day. The infection induced fever (>40.5 °C) in all animals, respiratory distress and reduced average daily weight gain and a mortality of up to 44%.
A second challenge study with a higher challenge titre of $10^{2.0}$ or $10^{4.0}$ $TCID_{50}$ was performed with a lower mortality (25%) but fever in all animals, and approximately 38% of the animals showed respiratory distress and weight loss. The strain originated from Belarus and was passaged on PAM for challenge stock preparation at the University of Ghent. The target titre of $10^{0.6}$ $CCID_{50}$/ml ($10^{0.9}$ $TCID_{50}$/dose of 2 ml) was back-titrated pre-challenge with $10^{1.8}$ $CCID_{50}$/ml and post-challenge with a titre of $10^{2.0}$ $CCID_{50}$/ml. This unexpectedly higher titre has been considered to be due to a technical issue, as the undiluted stock did fit the expected titre. An actual challenge titre of $10^{0.5}$ $CCID_{50}$/2 ml dose, derived from the calculated challenge dose of the stock and the dilution, has been stated. The titre used for challenge infection was justified and supported by published data, including study B821R-ES-17-757 for the development of the Lena strain challenge model in 4-week-old pigs.

Efficacy parameters and tests

The efficacy parameters as chosen by the applicant investigated in the efficacy studies were divided in **primary efficacy parameter** and **secondary efficacy parameters**.

The **primary efficacy parameter** was the evaluation of ***viraemia*** in serum samples, which were analysed by PRRSV-specific RT-qPCR. Validation studies on the specific RT-qPCR for the heterologous subtypes 1 to 3 were provided. For the studies evaluating the protection against heterologous PRRSV-1 subtypes, ***clinical observations*** were defined as primary efficacy parameter, except for the studies evaluating the efficacy of IN vaccination in 3-day old piglets.

The **secondary efficacy parameters** comprised rectal temperature, body weight, lung lesion and lung macroscopic lesion score (visual score), nasal and oral shedding and serology by ELISA. In addition, in study **B825R-AT-17-714**, lung microscopic lesion score (histology) and cell-mediated immunity (CMI) via ELISPOT assay were analysed. In the two studies (**B825R-ES-20-983** and

B828R-ES-20-A59) evaluating the efficacy of IN vaccination in 3-day old piglets, clinical observations were listed among the secondary efficacy parameters.

Efficacy documentation

Two studies (**B825R-ES-20-983** and **B825R-ES-20-A59**) were conducted to investigate the efficacy of Suvaxyn PRRS MLV after IN administration. The studies were carried out in 2- to 4-day old piglets, which should be included as the target species for the IN administration of Suvaxyn PRRS MLV.

Three studies were conducted to investigate the efficacy of Suvaxyn PRRS MLV after IM administration to 1-day old piglets to evaluate the efficacy against heterologous PRRSV-1 subtypes four weeks after vaccination. The heterologous PRRSV-1 challenge viruses evaluated were: subtype-1 AUT-15-33 in study **B825R-AT-17-714**, subtype-2 BOR57 in study **B825R-GB-17-715** and subtype-3 Lena in study **B825R-ES-17-716**.

Study reference	Study title
Evaluation of the efficacy of the intranasal administration route	
B825R-ES-20-983	Evaluation of the Onset of Immunity of Suvaxyn PRRS MLV in piglets vaccinated at three days of age by intranasal route
B825R-ES-20-A59	Assessment of the potential effect of maternally derived antibodies on the efficacy of the Suvaxyn® PRRS MLV administered to 3-day old seropositive pigs by intranasal route
Evaluation of protection against heterologous PRRSV-1 subtypes	
B825R-AT-17-714	Efficacy of Suvaxyn® PRRS MLV administered to 1-day-old pigs in front of the challenge with the heterologous PRRSV-1 subtype-1 AUT15-33 strain
B825R-GB-17-715	Efficacy of Suvaxyn® PRRS MLV administered to 1-day-old piglets in front of the challenge with the heterologous PRRSV-1 subtype2 BOR57 strain
B825R-ES-17-716	Efficacy of Suvaxyn® PRRS MLV administered to 1-day-old piglets in front of the challenge with the heterologous PRRSV-1 subtype-3 Lena strain

Pre-clinical studies

Dose determination

The minimum protective dose of 2.2 $\log_{10}$ $CCID_{50}$/dose has already been established during the marketing authorisation procedure of Suvaxyn PRRS MLV. This minimum protective dose of Suvaxyn PRRS MLV has been used in all of the five studies provided with the documentation for this grouped variation procedure.

Onset of immunity

Evaluation of protection against heterologous PRRSV-1 subtypes

The following three studies were provided to support the efficacy of Suvaxyn PRRS MLV applied intramuscularly in 1-day old piglets against three different heterologous PRRSV-1 subtypes in compliance with Ph. Eur. 50207.

In study **B825R-AT-17-714** - 'Efficacy of Suvaxyn® PRRS MLV administered to 1-day-old pigs in front of the challenge with the heterologous PRRSV-1 subtype-1 AUT15-33 strain', 48 seronegative piglets at the age of 1 day (24±12 hours) were used. A vaccine dose of the minimum protective dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was administered intramuscularly to group T02, and group T01 was treated with saline diluent, as an unvaccinated control. Both groups comprised 24 animals. All animals of both groups were challenged with virulent PRRSV-1 subtype-1 AUT15-33, 4 weeks (26–28 days) after vaccination. The primary efficacy parameter evaluated were viraemia (virus load in serum samples) and clinical observations. The following secondary efficacy parameters were evaluated: body weight, lung lesion, lung macroscopic and microscopic lesion score, nasal and oral shedding and rectal temperature. Furthermore, serology and cell-mediated immunity were evaluated.

Results: Significantly higher ($p<0.0001$) viral loads in serum were detectable in control animals compared to vaccinated piglets at all time points investigated following challenge infection (day 3, 5, 7, 10 and 13/14). Mean AUC values of RNA copies in serum were significantly lower ($p<0.0001$) in vaccinated animals and the mean percentage of days monitored when an animal was viraemic (ever viraemic analysis, T01 vs. T02 – 55.14% vs. 19.57%) was lower, too. Significantly lower clinical signs associated with PRRSV infection (depression, $p=0.0270$ and respiratory distress $p=0.0420$) were observed after challenge infection in vaccinated compared to control animals. No significant difference was observed for least square mean (LSM) of body weight before and after challenge between both groups. Nevertheless, the ADG from challenge until the end of the study was significantly lower in control animals compared to the vaccinated group (T01 vs. T02, 0.17 kg vs. 0.24 kg). Significant differences ($p=0.0124$) were observed between groups in the percentages of total lung with lesions; these were lower in the vaccinated compared to control animals. However, no significant treatment effect ($p\geq0.05$) was observed in lung lesion assessment score (visual score) between groups. Nevertheless, significantly lower percentage of vaccinated piglets showed intra-alveolar accumulation of inflammatory cells ($p=0.0486$) and presence of necrotic debris ($p=0.0258$) in the lung microscopic lesion score and a lower total score sum. Significantly higher ($p\leq0.05$) viral loads in nasal swab samples were detected in control piglets compared to vaccinated animals on days 3, 5 and 13/14 post infection. Mean AUC value of log viral loads in nasal secretions was significantly higher ($p<0.0001$) in control compared to vaccinated piglets (T01 vs. T02, 6.42±0.08 vs. of 5.96±0.08) over the whole post-challenge period. No significant differences ($p>0.05$) were observed for viral loads in oral secretions between groups at all time points investigated after challenge infection, including the mean AUC values. Significantly higher ($p\leq0.05$) mean rectal temperature was observed in control animals on days 2, 8 and 9 days after infection (days 30, 36 and 37), but no fever in mean rectal temperatures (RT>40.5 °C) was observed in any piglet of both groups. Only for the "ever fever analysis" it is stated that 85.0% of the control and 71.4% of the vaccinated animals showed ever fever at the investigated time points, but no significance is mentioned. Cell-mediated immunity (CMI) showed higher number of IFNγ-secreting cells in vaccinated animals in comparison to control animals at all time points monitored, and a significant negative correlation ($p<0.0001$) could be shown between the number of IFNγ-secreting cells and viraemia at days 7 and 13/14 post challenge (-0.70 and -0.65). Serology data confirmed that animals were seronegative prior to vaccination; these were still seronegative at the day of challenge, whereas immunised animals had responded to vaccination.

It was concluded that vaccination by the IM route with a minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was efficacious against challenge infection with PRRSV-1 subtype-1 AUT15-33 strain four weeks post-vaccination and did meet the efficacy requirements, except for oral shedding and lung lesion assessment score.

The efficacy claims in the SPC regarding the demonstration of protection against heterologous PRRSV-1 subtype-1 AUT15-33 strain applied 4 weeks post vaccination have been supported by the results of this study (SPC section 4.2). Intramuscular vaccination of seronegative 1-day old piglets with

Suvaxyn PRRS MLV conferred a reduction of viraemia, clinical signs (depression and respiratory distress), average daily weight losses, lung lesions (percentage of total lung with lesion), nasal shedding and rectal temperature. No differences were observed in oral shedding and lung lesion assessment score (visual score).
Information on the challenge model, as well as the validation study for the PRRSV-1 AUT15-33-specific RT-qPCR were provided. The applicant has included the information on the protection against subtype-1 AUT15-33 to SPC section 5 as "Additional studies", as the duration of immunity was not supported by any data. Information regarding the onset of immunity (OOI) of 28 days has been included, as well as the serological status of the target animals as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

In study **B825R-GB-17-715** - **'**Efficacy of Suvaxyn® PRRS MLV administered to 1-day-old piglets in front of the challenge with the heterologous PRRSV-1 subtype2 BOR57 strain', two groups of 22 one-day old seronegative piglets were used. A vaccine dose of the minimum protective dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was administered intramuscularly to group T02, and group T01 was treated with saline diluent, as an unvaccinated control. All animals of both groups were challenged with virulent PRRSV-1 subtype-2 BOR57 strain 4 weeks (26-28 days) after vaccination. The primary efficacy parameter evaluated were viraemia (virus load in serum samples) and clinical observations. The following secondary efficacy parameters were evaluated: body weight, lung lesion, lung macroscopic lesion score, nasal and oral shedding, rectal temperature and serology.

Results: Significantly lower ($p \leq 0.5$) viral loads were observed in the vaccinated compared to the control piglets on day 2, 4, 6 and 8 post-challenge. Mean AUC values for PRRSV-1 subtype-2 BOR57 viral loads were significantly lower ($p<0.0001$) in immunised animals compared to controls for the complete post-challenge period of the study. In clinical observations, significant differences were observed for abnormal demeanour and abnormal respiration, which were lower in vaccinated animals compared to controls (T01 vs T02, 22.7% vs 4.5% and 4.5% vs. 0.0%), but significance was only stated in the abstract of the study. Average daily weight gain (ADG) from challenge until the end of the study was significantly lower in the control animals compared to vaccinated piglets (T01 vs. T02, 0.03 kg vs. 0.20 kg). Significantly lower ($p=0.008$) percentage of lungs with lesion were observed in vaccinated piglets compared to control animals (T01 vs. T02, 15% vs. 3%), as well as the percentage of animals that had a positive lung score at the end of the study ($p=0.0054$, T01 vs. T02, 63.6% vs. 18.2%). No significant differences ($p>0.05$) were observed between both groups for nasal shedding. Significantly higher ($p \leq 0.05$) viral loads in oral swab samples were observed in control compared to vaccinated piglets at day 6 and 10 post infection and mean AUC of log viral loads was significantly higher ($p=0.0059$) in vaccinated animals compared to controls. Serology data confirmed that animals were seronegative prior to vaccination; these were still seronegative at the day of challenge, whereas immunised animals had responded to vaccination. Significant differences in PRRSV-specific antibodies in serum were observed between both groups at day 27/28 (before challenge, $p=0.0001$) and day 37/38 (end of study, p=00036).

It was concluded that vaccination by the IM route with a minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was efficacious against challenge infection with PRRSV-1 subtype-2 BOR57 strain four weeks post-vaccination and did meet the efficacy requirements, except for nasal shedding and rectal temperatures.

The efficacy claims in the SPC regarding the demonstration of cross protection against heterologous PRRSV-1 subtype-2 BOR57 strain applied 4 weeks post vaccination have been supported by the results of this study (SPC section 4.2). Intramuscular vaccination of seronegative 1-day old piglets with

Suvaxyn PRRS MLV conferred a reduction of viraemia, clinical signs (demeanour and abnormal respiration), average daily weight losses, lung lesions and lung lesion assessment score and oral shedding. No differences were observed in nasal shedding and rectal temperatures.

Information on the challenge model, as well as the validation study for the PRRSV-1 subtype-2 BOR57-specific RT-qPCR was provided. Information on the protection against subtype-2 BOR57 to SPC section 5 is added as "Additional studies" as the duration of immunity was not supported by any data. Information on the onset of immunity of 28 days has been included, as well as the serological status of the animals as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

In study **B825R-ES-17-716** - 'Efficacy of Suvaxyn PRRS MLV administered to 1-day-old piglets in front of the challenge with the heterologous PRRSV-1 subtype-3 Lena strain', 54 one-day old seronegative piglets were used. A vaccine of the minimum protective dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was administered intramuscularly to group T02 with 29 piglets, and group T01 with 25 piglets (24 piglets - one was found dead under the sow after treatment) was treated with saline diluent, as an unvaccinated control. All animals of both groups were challenged with virulent PRRSV-1 subtype-3 Lena strain four weeks (26-28 days) after vaccination. The primary efficacy parameter evaluated were viraemia (virus load in serum samples) and clinical observations. The following secondary efficacy parameters were evaluated: body weight, lung lesion, lung macroscopic lesion score, nasal and oral shedding, rectal temperature and serology.

Results: Significantly lower ($p \leq 0.05$) viral loads were observed in vaccinated animals 10 days post-challenge (day 37), as well as significantly lower ($p < 0.001$) mean AUC log viral loads in vaccinated animals compared to control piglets. Statistically significantly more ($p = 0.0074$) animals of the control group showed depression during the whole post-challenge phase compared to vaccinated animals (T01 vs. T02, 70.8% vs. 31%). No significant differences were observed for the other clinical signs between both groups. Average daily weight gain from challenge until the end of the study was significantly higher ($p \leq 0.05$) in vaccinated animals compared to controls (T01 vs. T02, 0.12 kg vs. 0.22 kg). Significantly lower ($p = 0.0303$) percentages of total lung with lesions were observed in vaccinated compared to control animals, but differences in lung lesion assessment score (visual score) were not significant ($p = 0.0865$). Differences were observed in viral loads in nasal swab samples on day 30 and 34 (3 and 7 days post-challenge) which were significantly higher ($p \leq 0.05$), but significantly lower ($p \leq 0.05$) on day 32 (5 days post-challenge) in control animals compared to vaccinated piglets. Therefore, no significant difference ($p > 0.05$) was observed for nasal shedding by mean AUC of log viral loads over the whole post-challenge phase between groups. Significantly lower ($p \leq 0.05$) viral loads in oral swab samples were observed in control animals on day 30 and 37 (3 and 10 days post-challenge) and mean AUC value was significantly lower ($p = 0.0138$) in control animals, too, compared to vaccinated animals. Mean rectal temperatures were significantly higher ($p \leq 0.05$) on day 36 and 37 (8 and 9 days post-challenge) in control compared to vaccinated animals; at all other time points no significant difference ($p > 0.05$) was observed. No differences were observed in the "ever fever analysis" between groups but when fever was analysed on a daily basis, results revealed that significantly lower percentage of vaccinated animals showed fever on day 3 and 10 post-challenge ($p = 0.0264$ and $p = 0.0117$) compared to control piglets. Serology results confirmed that all animals were seronegative before vaccination and that piglets in the vaccinated group had responded to immunisation with Suvaxyn PRRS MLV.

It was concluded that vaccination by the intramuscular route with a minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was efficacious against challenge infection with PRRSV-1 subtype-3 Lena strain

four weeks post-vaccination and did meet the efficacy requirements, except for shedding and lung lesion assessment score (visual score).

The efficacy claims in the SPC regarding the demonstration of cross protection against heterologous PRRSV-1 subtype-3 Lena strain applied 4 weeks post vaccination have been supported by the results of this study (SPC section 4.2). Intramuscular vaccination of seronegative 1-day old piglets with Suvaxyn PRRS MLV conferred a reduction in viraemia, clinical signs (depression), average daily weight losses, rectal temperatures and lung lesions. No differences were observed in shedding and lung lesion assessment score (visual score).
Additional information on the challenge model as well as for the PRRSV-1 subtype-3 Lena-specific RT-qPCR was provided. Information on the protection against subtype-3 Lena strain to SPC section 5 is added as "Additional studies" as the duration of immunity was not supported by any data. Information on onset of immunity of 28 days has been included, as well as the serological status of the animals as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

Evaluation of the efficacy of the nasal administration route

The following study (**B825R-ES-20-983)** was provided to support the efficacy of Suvaxyn PRRS MLV applied by the IN route to 3- to 4-day old piglets against PRRSV-1 isolate Olot/91. This challenge strain was already used for the studies provided with the marketing authorisation dossier of Suvaxyn PRRS MLV. The study was carried out in compliance with Directive 2009/9/EC and Ph. Eur. 50207. Additionally, it is stated that the facility at Zoetis in Spain is AAALAC accredited.

In study **B825R-ES-20-983 -** 'Evaluation of the Onset of Immunity of Suvaxyn PRRS MLV in piglets vaccinated at three days of age by intranasal route', 44 piglets 3 to 4 days of age, serologically negative to PRRSV, were used. A vaccine of the minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was administered by the IN route to group T02 with 29 piglets, and group T01 with 24 piglets was treated with saline diluent, as an unvaccinated control. All animals of both groups were challenged with virulent PRRSV-1 Olot/91 strain 3 weeks (21 days) after vaccination. The primary efficacy parameter evaluated were viraemia (virus load in serum samples). The following secondary efficacy parameters were evaluated: lung lesion, lung lesion assessment score (visual score), nasal and oral shedding, rectal temperature, clinical observations and serology. No clinical signs before or after challenge were observed in any of the piglets (except one control animal with a score of 1 on day 31).

Results: Significantly lower ($p \leq 0.0330$) viral loads were observed in serum samples of vaccinated animals compared to controls on days 2, 4, 7 and 10 post-challenge (days 23, 25, 28 and 31) as well as a significantly lower ($p < 0.0001$) mean AUC of log viraemia. Significantly lower percentage ($p = 0023$) of total lung with lesions at the end of the study and significantly lower ($p = 0.0029$) percentage of animals scored positive were observed in vaccinated compared to control piglets. Significantly lower ($p < 0.0001$) viral loads in nasal swab samples were detected in vaccinated compared to control piglets on days 2, 4 and 7 post-challenge (days 23, 25 and 28), as well as significantly lower ($p < 0.0001$) mean AUC values of log viraemia were observed in the immunised group. Significantly lower ($p \leq 0.05$) viral loads were also detected in oral swab samples on days 4 and 7 post-challenge (days 25 and 28) in the vaccinated animals, but the mean AUC values of log viraemia were not significantly different between groups. No significant differences ($p > 0.05$) in rectal temperatures or pigs that ever had a fever in the post-challenge period were observed between both groups. Significantly higher ($p \leq 0.05$) body weight means were observed in vaccinated piglets before challenge and at the end of the study; consequently, the average daily weight gain (ADG) was significantly higher ($p = 0.0245$) in vaccinated animals compared to controls (T01 vs. T02, 0.11 kg vs. 0.15 kg). Serology data confirmed that animals were seronegative at birth and prior to vaccination.

Before challenge (day 21), control piglets were still seronegative at the day of challenge, whereas immunised animals had responded to vaccination. Significantly higher ($p<0.0001$) mean antibody levels were detected in vaccinated animals compared to controls at the day of challenge and at the end of the study.

It was concluded that IN vaccination with Suvaxyn PRRS MLV applied to 3-day old seronegative piglets was efficacious against challenge infection with PRRSV-1 Olot/91 strain at 21 days post-vaccination. Vaccination has significantly reduced viraemia, nasal shedding, lung lesion score and percentage of lung with lesions. Furthermore, a significantly higher body weight and average daily weight gain (ADG) were observed in vaccinated animals. No differences were observed in rectal temperatures or oral shedding.

Changes in the SPC regarding the demonstration of the efficacy of the IN administration to piglets from 3-day old onwards are in line with the results in the study. In section 4.9 of the SPC, the method of administration and the dosage has been amended as "nasal administration: 2 ml administered as 1 ml in each nostril". For the 'Vaccination schedule', a differentiation was made. "Pigs for fattening from 1 day of age onwards" should be vaccinated "via intramuscular administration". "Pigs for fattening from 3 days of age onwards" should receive "A single dose of 2 ml is given to pigs via intramuscular administration, or a single dose of 2 ml is given to pigs via nasal route by administering 1 ml in each nostril using a sterile syringe not connected to a needle", as shown by the data provided. Furthermore, for "gilts and sows" the wording "intramuscularly" has been added for the advice on the 'vaccination schedule". The statement, "Additionally, nasal vaccination of seronegative 3-day-old piglets reduced viraemia, nasal shedding and lung lesions against challenge administered at 21 days post-vaccination. Nasal vaccination of seropositive 3-day-old piglets reduced viraemia, nasal shedding and lung lesions against challenge administered 10 weeks post-vaccination." in section 4.2 of the SPC is in line with the results of the study provided. A significant reduction in viraemia, nasal shedding and lung lesions of the nasal administration in 3-day old piglets has been adequately shown by the data provided. An onset of immunity of 3 weeks was shown in seronegative piglets and the following warning has been included in section 4.4 of the SPC: "Do not vaccinate pigs younger than 3 days by nasal route since the concurrent intake of colostrum may interfere with the efficacy of the vaccine."

Duration of immunity

Evaluation of protection against heterologous PRRSV-1 subtypes

The duration of immunity (DOI) for the protection against heterologous PRRSV-1 subtypes was not evaluated. The provided studies analysed an onset of immunity of 4 weeks in 1-day old piglets vaccinated intramuscularly with Suvaxyn PRRS MLV, followed by a challenge with one of the PRRSV-1 subtypes: subtype 1 AUT15-33, subtype 2 BOR57 or subtype 3 Lena. Information on the protection against heterologous PRRSV-1 subtypes has been included in SPC section 5 as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

Evaluation of the efficacy of the nasal administration route

The duration of immunity (DOI) was already assessed during the original marketing authorisation procedure for the intranasal route in 1-day old piglets. Studies **B824R-ES-14-437** and **B824R-ES-14-438** provided with the original documentation for marketing authorisation of Suvaxyn PRRS MLV evaluated the DOI in 1-day old seronegative respectively seropositive piglets, followed by a challenge infection with PRRSV-1 Olot/91 strain applied 18 weeks, respectively 26 weeks after intranasal

vaccination, with a dose containing the minimum of 2.2 $\log_{10}$ $CCID_{50}$. Results of both studies revealed that vaccinated animals showed reduced viraemia, reduced nasal and oral shedding and reduced lung lesions after challenge infection. Therefore, a DOI of 26 weeks is acceptable for the nasal administration route.

NOTE: See also results from study **B828R-ES-20-A59** - 'Assessment of the potential effect of maternally derived antibodies on the efficacy of the Suvaxyn PRRS MLV administered to 3-day old seropositive pigs by intranasal route" in which the nasal administration route with a subsequent challenge with PRRSV-1 Olot/91 strain approximately 10 weeks after vaccination was evaluated (see below).

Maternally derived antibodies (MDA)

One study was carried out in seropositive piglets to investigate the potential influence of MDAs on the protective capacity of the nasal administration route in 2- to 3-day old piglets. The study was carried out in compliance with Directive 2009/9 EC, Ph. Eur. 50207 and EMA/CVMP/IWP/439467/2007: 'Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals'.

In study **B828R-ES-20-A59** – 'Assessment of the potential effect of maternally derived antibodies on the efficacy of the Suvaxyn® PRRS MLV administered to 2- to 3-days-old seropositive pigs by intranasal route', 60 seropositive piglets derived from 6 sows, which were vaccinated with Suvaxyn PRRS MLV during the first half of gestation (day 41), were used. A vaccine of the minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was administered by IN administration to group T02 with 32 piglets, and group T01 with 28 piglets was treated with saline diluent, as an unvaccinated control. All animals of both groups were challenged with virulent PRRSV-1 Olot/91 strain 69 days later (approx. 10 weeks), when maternally derived antibodies had declined to undetectable titres by serum neutralisation test (SNT titre ≤2) in the control group. The primary efficacy parameter evaluated was viraemia (virus load in serum samples). The following secondary efficacy parameters were evaluated: lung lesion, lung lesion assessment score (visual score), nasal and oral shedding, rectal temperature, clinical observations, body weight and serology.

Results: Significantly lower ($p \leq 0.05$) viral loads were observed in vaccinated animals on day 5 and 7 post-challenge compared to control animals, but on day 2 and 9 post-challenge differences between groups were not significant ($p > 0.05$). Nevertheless, the mean AUC value of log viral loads was significantly lower ($p < 0.0001$) in vaccinated piglets compared to control. Significantly lower ($p = 0.0175$) percentage of total lung with lesions was observed in the vaccinated group compared to the control group (T01 vs. T02, 3.42 vs. 1.36) and a significantly lower ($p = 0.0265$) percentage of animals was also scored positive (score>0) in vaccinated animals compared to controls. None of the vaccinated animals showed a lung visual score of 2 compared to 10.7% of the control piglets. Significantly lower ($p < 0.0001$) viral loads were detectable in nasal swab samples of vaccinated piglets at days 5 and 7 post-challenge, but viral loads were significantly higher ($p = 0.0018$) in the vaccinated group two days post-challenge compared to controls. Differences in viral loads in nasal secretions were not significantly different ($p > 0.05$) between groups at the end of the study (day 78). However, the mean AUC value of log viral loads in nasal swab samples was significantly lower ($p < 0.0001$) in the vaccinated compared to the control group. Again, significantly lower ($p \leq 0.05$) viral loads were detectable in oral swab samples of vaccinated piglets on day 5 and 7 post-challenge, but viral loads were significantly higher ($p \leq 0.05$) in the vaccinated group on day 2 post-challenge compared to controls. Similar to the results of nasal shedding, differences between both groups were not significant at the end of the study (day 78). However, mean AUC values of log viral loads in oral secretions were

significantly lower (p=0.0212) in vaccinated animals compared to controls. Differences in mean rectal temperatures between groups were not significant (p>0.05) in the whole challenge phase. Although a significantly higher (p=0.0007) mean rectal temperature was observed in control animals at 5 days post-challenge, no animal showed fever (RT>40.5 °C) on that day. In the post-challenge phase, no clinical observations were observed, except for one piglet of the control group (#913), which was scored abnormal due to lameness on days 7 and 9 post-challenge. No significant differences were observed in mean body weight between groups before challenge (day 69, T01 vs. T02, 33.01 kg vs. 33.92 kg) and at the end of the study (day 78, T01 vs. T02, 39.95 kg vs. 39.47 kg). However, calculation of the difference of mean average daily weight gain (ADG) from challenge until the end of the study revealed significantly higher (p=0.0226) ADG in control animals compared to vaccinated piglets in favour of the control group (difference of 0.14 kg/day, T01 vs. T02, 0.69 kg vs. 0.56 kg).

Serology data confirmed that animals were seropositive prior to treatment with the vaccine or saline diluent, except for four piglets (T01 group: #908, 1027, 944 and T02 group: #942), which were successfully verified to be positive by serum neutralisation test (SNT). At day 62, control piglets were tested negative for neutralising antibodies by SNT and the animals were challenged one week later (day 69). At the end of the study (day 78), mean PRRSV-specific antibodies measured by ELISA (S/P ratio>0.4) were significantly higher (p<0.0001) in vaccinated compared to control animals.

It was concluded that vaccination of seropositive 2- to 3-day old piglets by the IN route with a minimum dose of $10^{2.2}$ $TCID_{50}$ of Suvaxyn PRRS MLV was efficacious against challenge infection with PRRSV-1 Olot/91 strain sixty-nine days post-vaccination and did meet the efficacy requirements. This was shown by a reduction of viraemia, lung lesion score and percentage of lung with lesions and shedding (oral and nasal). No differences were observed between groups for rectal temperature, clinical observations or least square means body weight at challenge and the end of the study, although a significant difference in ADG (from challenge until the end of study) was observed in favour of the control animals.

Efficacy claims in the SPC regarding the IN administration to seropositive piglets from 3-day old onwards are in line with the results of the study. In section 4.2 of the SPC, a slight rewording has been proposed instead of "Additionally, after nasal vaccination a reduction in viraemia, nasal shedding and lung lesions was observed in seronegative 3-day old piglets against challenge administered at 21 days post-vaccination and in seropositive 3-day old piglets against challenge administered 10 weeks post-vaccination.". The applicant proposed the following wording "Additionally, nasal vaccination of seronegative 3-day-old piglets reduced viraemia, nasal shedding and lung lesions against challenge administered at 21 days post-vaccination. Nasal vaccination of seropositive 3-day-old piglets reduced viraemia, nasal shedding and lung lesions against challenge administered 10 weeks post-vaccination.", which is acceptable. A warning in SPC section 4.4. regarding the possible interference of MDAs with vaccine efficacy/onset of immunity has been included, as follows: "Do not vaccinate pigs younger than 3 days by nasal route since the concurrent intake of colostrum may interfere with the efficacy of the vaccine.". Regarding the onset of immunity in seropositive piglets, the applicant provided a sufficient justification. In combination with the inclusion of the newly proposed warning in section 4.4., this issue has been satisfactorily solved. The duration of immunity has been adequately shown in seronegative and seropositive piglets, and is acceptable.

Interactions

Suvaxyn PRRS MLV is not intended to be used concomitantly with other vaccines; therefore, this section is not applicable.

Clinical trials

No clinical trials were provided with the documentation for this grouped variation procedure.

Overall conclusion on efficacy

Regarding the cross-protection against heterologous PRRSV-1 subtypes, the results from three pre-clinical studies show that efficacy requirements were met when Suvaxyn PRRSV MLV is administered intramuscularly to 1-day old seronegative piglets at the minimum dose of $10^{2.2}$ $TCID_{50}$. The vaccine is effective in reducing viraemia, lung lesion and loss of average daily weight gain following a challenge 4 weeks after vaccination with either subtype-1 AUT15-33, subtype-2 BOR57 or subtype-3 Lena. The protection against the heterologous PRRSV-1 subtypes has been included in SPC section 5 as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

The product has been shown to have an onset of immunity 4 weeks after IM vaccination against heterologous PRRSV-1 subtypes, which was demonstrated in seronegative 1-day old piglets (fattening pigs). The data only support efficacy in seronegative piglets (pigs for fattening). No data have been provided to support the efficacy in gilts and sows and the prevention of transplacental transmission after challenge infection with the three different PRRSV-1 subtypes. As no supportive data have been provided for the duration of immunity regarding the cross-protection against the three heterologous PRRSV-1 subtypes, no information has been therefore included in the SPC.

Regarding the efficacy of the nasal administration route in piglets from 3 days of age onwards, the results from two laboratory studies show that Suvaxyn PRRS MLV administered to 3-day old piglets with a minimum dose of $10^{2.2}$ $TCID_{50}$ by the nasal route met the efficacy requirements against PRRSV-1 Olot/91 challenge. This was shown by a reduction of viraemia, lung lesions score and percentage of lungs with lesions and nasal shedding after challenge infection.

The product has been shown to have an onset of immunity 3 weeks after vaccination, which was demonstrated in seronegative 3-day old piglets (pigs for fattening). MDAs did not interfere with vaccination if the challenge was applied 69 days later; the timepoint at which MDAs were low-to-not-detectable anymore in the non-vaccinated control group is in line with EMA/CVMP/IWP/439467/2007 "Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals". A sufficient justification including a warning under SPC section 4.4 was provided. The duration of immunity of 26 weeks for the nasal administration route in seropositive animals was considered acceptable.

Part 5 – Benefit-risk assessment

Introduction

Suvaxyn PRRS MLV is already authorised for intramuscular use in pigs for active immunisation of clinically healthy pigs from 1 day of age in a porcine respiratory and reproductive syndrome (PRRS) virus-contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1). Suvaxyn PRRS MLV lyophilisate and solvent for suspension for injection for pigs contains $10^{2.2}$ – $10^{5.2}$ $CCID_{50}$ of modified live PRRSV, strain 96V198. It is presented in packs containing one glass vial of 15 ml of lyophilisate (25, 50 or 125 doses) and one HDPE vial of 50, 100 or 250 ml of solvent.

The proposed variation is to add nasal use as an additional route of administration and to modify the approved therapeutic indication to include protection against heterologous subtype-1 AUT15-33, subtype-2 BOR57 and subtype-3 Lena strains of the PRRS virus.

The new nasal application route for piglets from 3 days of age onwards, in addition to the intramuscular application route for piglets from 1 day of age onwards, has been shown to be efficacious. The onset of immunity in seropositive animals has been sufficiently justified and a warning on the influence of MDAs in relation to the uptake of colostrum and possible interference with vaccine efficacy has been included in SPC section 4.4. in context with nasal administration route in piglets younger than 3 days.

The protection against heterologous subtypes in 1-day old piglets after a single intramuscular immunisation with Suvaxyn PRRS MLV at the minimum protective dose has been satisfactorily shown against all three different subtypes. The proposed indication for protection has been included in section 5 of the SPC with an onset of immunity of four weeks, supported by the results provided. No duration of immunity has been evaluated for the protection against heterologous subtypes of PRRSV-1 and therefore no information has been included in the SPC. However, a revised wording has been proposed to include only essential information on the protection against other PRRSV-1 subtypes as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

The nasal administration of Suvaxyn PRRS MLV to 3-day old piglets provides a gentle vaccine application method and an alternative to the intramuscular administration, without the induction of adverse reactions at the injection site.

Benefit assessment

Direct benefit

Suvaxyn PRRS MLV is efficacious in the reduction of viraemia and nasal shedding in a porcine respiratory and reproductive syndrome (PRRS) virus-contaminated environment to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1).

With this variation, the nasal use as an additional route of administration for piglets (pigs for fattening) of 3 days of age was investigated in two pre-clinical studies (one OOI study, one MDA study), conducted to an acceptable standard. Concerns about the onset of immunity in seropositive pigs have

been sufficiently justified and a warning on interference with vaccine efficacy and colostrum intake in piglets younger than 3 days in context with nasal administration of the vaccine has been included.

Further, the protection against subtype-1 AUT15-33, subtype-2 BOR57 and subtype-3 Lena strains of the PRRS virus was investigated in three pre-clinical studies in seronegative piglets immunised intramuscularly at 1 day of age, which were conducted to an acceptable standard. This information was included in SPC section 5 as follows: "Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

Additional benefits

The nasal administration of Suvaxyn PRRS MLV is considered in general a gentle application route for piglets at a young age of 3 days, except for the necessity of more restraining in comparison with the intramuscular administration route.

Risk assessment

Quality

Quality remains unaffected by this variation.

Safety

Safety (user, consumer, environmental, target animal) remains unaffected by this variation.

Risks for the target animal

Administration of Suvaxyn PRRS MLV in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions are not affected by this variation, as the vaccine is applied by the nasal route to piglets of 3 days of age, without any local tissue reactions to be expected as for the intramuscular administration route. The potential for mild and transient adverse effects, such as transient increase in rectal temperature after vaccination, cannot be excluded as for intramuscular application. A warning that vaccinated animals may excrete the vaccine strain for more than 16 weeks following vaccination has already been included in the SPC during marketing authorisation procedure in 2017, and an additional warning regarding the excretion of the vaccine strain after nasal administration for more than 10 weeks has been included.

Risk for the user

The user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment

Suvaxyn PRRS MLV is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC. A warning has been included to limit the risk of recombination between PRRS vaccine strains: "In order to limit the potential risk of recombination between PRRS MLV vaccine strains of the same genotype, do not use different PRRS MLV vaccines based on different strains of the same genotype on the same farm at the same time. In the case of transitioning from one PRRS MLV vaccine to another PRRS MLV vaccine, a transition period should be respected between the last administration of the current vaccine and the first administration of the new vaccine. This transition period should be longer than the shedding

period of the current vaccine following vaccination. Do not routinely rotate two or more commercial PRRS MLV vaccines based on different strains in a herd."

Risk for the consumer:

The risk for the consumer is not affected by this variation.

Special risks

No special risk concerns are related to this variation.

Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation. The product information has been updated according to the outcome of the article 35 referral on PRRS MLV vaccines (EMEA-V-A-142).

Consequently, appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment, and to provide advice on how to prevent or reduce these risks. The shedding period linked to the intranasal and/or intramuscular administration has been specified with an appropriate amendment of SPC section 4.5. as follows:
"Animals vaccinated via intramuscular route may excrete the vaccine strain for more than 16 weeks following vaccination. Animals vaccinated via nasal route may excrete the vaccine strain for more than 10 weeks.".

Evaluation of the benefit-risk balance

The changes described in this variation are not envisaged to impact on quality, safety, user safety, environmental safety, consumer safety and target animal safety.

The product has been shown to be efficacious after nasal administration to pigs for fattening from 3 days of age onwards, in addition to the intramuscular administration for pigs for fattening from 1 day of age onwards:
"For active immunisation of clinically healthy pigs from 1 day of age in a porcine respiratory and reproductive syndrome (PRRS) virus-contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1)."

Additional information for fattening pigs has been included and revised under section 4.2 as follows:

Fattening pigs:

In addition, intramuscular vaccination of seronegative 1-day-old piglets was demonstrated to reduce lung lesions against challenge administered at 26 weeks post vaccination. Intramuscular vaccination of seronegative 2-week-old piglets was demonstrated to reduce lung lesions and oral shedding against challenge administered at 28 days and at 16 weeks post-vaccination.

Additionally, nasal vaccination of seronegative 3-day-old piglets reduced viraemia, nasal shedding and lung lesions against challenge administered at 21 days post-vaccination. Nasal vaccination of seropositive 3-day-old piglets reduced viraemia.

Based on the data presented to date, the overall benefit-risk balance for the variation is considered positive.

The product information has been reviewed. The proposed wording has been included as follows:
"Additional clinical studies demonstrated that intramuscular vaccination of seronegative 1-day-old

piglets conferred protection against another subtype-1 strain (AUT15-33), a subtype-2 strain (BOR57) and a subtype-3 strain (Lena) of PRRS virus genotype 1."

Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Suvaxyn PRRS MLV is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the approval of the variation for the above mentioned veterinary medicinal product.