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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP assessment report for a grouped type II variation for Suvaxyn PRRS MLV (EMEA/V/C/004276/II/0004/G)

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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# 1. Introduction

## *1.1. Submission of the variation application*

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder (MAH), Zoetis Belgium SA, submitted to the European Medicines Agency (the Agency) on 12 October 2018 an application for a grouped type II variation for Suvaxyn PRRS MLV.

## *1.2. Scope of the variation*

| **Variations requested** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. Reduce the onset of immunity. | II |
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. Extend the duration of immunity. | II |
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one. Reduction of body weight losses of piglets born from vaccinated gilts or sows at weaning. | II |
| C.I.6.z | Change(s) to therapeutic indication(s) - Other variation. Changes to the immunological status of gilts and sows at the time of vaccination and changes to the use during lactation. | IB |

The variation is to reduce the onset of immunity (OOI), extend the duration of immunity (DOI) and introduce an additional indication (reduction of body weight losses of piglets (born from vaccinated gilts/sows) at weaning). Additionally, the MAH proposes changes to the product information regarding the immunological status of gilts and sows at the time of vaccination and changes to the use during lactation. Finally, there are two editorial changes to the product information.

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

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

Part 1 and Part 4

## *1.4. Scientific advice*

Not applicable.

## *1.5. MUMS/limited market status*

Not applicable.

# 2. Scientific Overview

The applicant proposes to **reduce the OOI from 28 days to 21 days**. Therefore, a laboratory study "Evaluation of the Onset of Immunity of Suvaxyn PRRS MLV in piglets vaccinated at one day of age and challenged at three weeks post-vaccination" was conducted.

In this study 60 healthy piglets (mixed sex) from 6 sows were vaccinated intramuscularly with a minimum dose of Suvaxyn PRRS MLV (2.2 $\log_{10}$ $CCID_{50}$/dose of 2 ml) at an age of 1 day (24 ±12 hours). A challenge infection with EU PRRSV isolate Olot/91 was applied intranasally 21 days later. Results showed no abnormal clinical observation in any pig throughout the study and none of the pigs had fever before challenge. The percentage of piglets that had fever after challenge was not significantly different between control and vaccinated animals (76% vs. 68%). No significant differences were observed in lung scoring. However, differences were found for viral loads in nasal swabs and serum (viraemia) which were significantly lower in vaccinated animals on DC+3, DC+5 and DC+10 after challenge compared to control animals. No differences between both groups were found for oral shedding and for antibodies as all animals were seropositive to PRRSV 10 days after challenge (at necropsy).

In summary, a single vaccination with Suvaxyn PRRS MLV in one-day-old piglets followed by a challenge infection with an EU-PRRSV isolate three weeks later was able to reduce viraemia and nasal shedding in piglets as already stated in the SPC. Therefore, a reduction of OOI from 28 days to 21 days is sufficiently shown by this study.

The applicant additionally proposes to **extend the DOI of 16 weeks for sows to 26 weeks and change the single booster dose to be given every 4 months to every 6 months**. Therefore, two laboratory studies in sows "Duration of immunity (DOI) of the EU PRRS MLV administered in sows against reproductive challenge with a European PRRSV isolate six month after vaccination" and "Assessment of the Response to Booster of Suvaxyn PRRS MLV in Sows against Reproductive Challenge with a European PRRSV Isolate Seven Months after Booster Vaccination" were conducted.

In the first study, 18 female pigs older than 10 months and serologically negative to PRRSV were included. Nine sows were either vaccinated once with a minimum dose of Suvaxyn PRRS MLV (2.1 $\log_{10}$ $CCID_{50}$/dose of 2 ml) or with saline diluent as control. Sows were oestrus synchronised and mated 10 or 11 weeks post vaccination (D75 to D80) and challenged with an EU-PRRSV isolate on D161 (23 weeks post vaccination, lot 1) to D209 (30 weeks post vaccination, lot 2) after vaccination. There was no difference in pregnancy length between vaccinated and non-vaccinated sows. A significant higher percentage of piglets born alive, born healthy and weaned piglets were observed in vaccinated sows. No differences were detected in the number of mummies and of low-viable piglets between both groups. No sow from any group had fever throughout the whole study and mild clinical observations were observed in three control sows only after challenge. Lower viral loads in serum of vaccinated sows were detected on DC+2/3, DC+5/7 and DC+9/10 compared to control sows. This was also the case for viral loads in nasal fluids which were lower in vaccinated animals on DC+5/7 and for oral fluids on DC+2/3 compared to control sows. In piglets the viraemia at birth and at weaning was significantly lower in animals derived from vaccinated sows as well as the percentage of piglets found positive compared to piglets derived from control sows. In broncho-alveolar lavages (BAL), viral loads were significantly lower in piglets from vaccinates compared to control piglets. Clinical observations were significantly lower in vaccinated animals compared to control animals. The percentage of lung lesions in piglets from vaccinates was significantly lower at weaning and these lungs were only scored with mild lesions compared to piglets from controls. The study results support the extended DOI of 26 weeks in sows after a single vaccination with Suvaxyn PRRS MLV.

In the second study, again 18 female pigs older than 10 months and serologically negative to PRRSV were included. 9 sows were vaccinated twice at day 0 and day 168 (24 weeks interval) with the minimum dose

of Suvaxyn PRRS MLV (2.1 and 2.3 $\log_{10}$ $CCID_{50}$/dose of 2 ml). Control sows received saline diluent. Animals were oestrus synchronised and mated on D278 to D283. An intranasal challenge with EU PRRSV strain Olot was given intranasally on D362±1 after the first vaccination (approximately 28 weeks after the second vaccination and on day 79 to 84 of gestation). All sows had a normal pregnancy length range and no sow aborted. A higher percentage of piglets born alive was observed in vaccinated sows compared to control sows. No significant differences were found in rectal temperatures after challenge and only one sow of the vaccinated group had fever (DC+3). A higher proportion of sows with depression was found in the vaccinated group. Viral loads in serum of vaccinated sows were significantly lower after challenge infection compared to control animals (DC+3, DC+6 and DC+10). Viral loads in nasal fluids were significantly lower in vaccinated sows on DC+3 and DC+6 compared to control sows. No differences were observed for oral shedding. Viral loads in serum of piglets at birth and at weaning, in BALs at necropsy as well as the percentage of positive lungs were significantly lower in progenies of vaccinated sows compared to that of control sows. The percentage of lung lesions in piglets from vaccinates was significantly lower, and these lesions were only of mild score compared to control piglets. The percentage of piglets with abnormal clinical observations was not significantly different between both groups.

In summary, the results of this study show that a booster vaccination applied approximately 6 months after the first vaccination, followed by a challenge infection 7 months after the booster vaccination does reduce viraemia as well as nasal shedding in sows. A reduction of the transplacental infection caused by PRRS virus during the last third of pregnancy (significantly lower vireamia and lung lesions in piglets born from vaccinated sows) and a reduction of the associated negative impact on reproductive performance (higher percentage of piglets born alive) as stated in the SPC has also been shown. Finally, the study supports the extension of the DOI in sows from 16 weeks to 26 weeks as proposed by the applicant.

For the proposed claim of the **reduction of body weight loss in piglets at weaning** the applicant provided data from the two studies conducted to support the extension of the duration of immunity and response to booster, which showed that in total 153 piglets born from vaccinated sows had a significantly higher body weight at weaning compared to in total 131 piglets born from unvaccinated sows. The body weight range at weaning from progenies of vaccinated sows was 4.2 to 9.3 kg and 2.3 to 8.7 kg, compared to progenies of control sows which had a body weight range from 1.5 to 6.8 kg and 1.3 to 8.4 kg, respectively. The relevance of a short duration of the proposed secondary productivity efficacy claim and the proposed benefit of vaccination in terms of reduced weight loss was questionable. As no further data were available to support a reduction of body weight loss in piglets at weaning, the applicant withdrew the proposed claim.

The applicant additonally proposed **changes to the product information**regarding the immunological status of gilts and sows at the time of vaccination. The applicant proposed to exchange the wording **'seropositive sows'** to 'primed gilts and sows (previously immunised against EU-PRRS virus via vaccination or via field infection') and the wording **'seronegative sows'** to 'PRRS virus-naïve gilts and sows'.

The change in the wording 'seronegative sows' to 'PRRS virus-naïve gilts and sows' is considered acceptable. For the proposed change for 'seropositive sows' the applicant did perform a study that was part of the initial marketing approval dossier of Suvaxyn PRRS MLV. In this study sows had been tested negative by RT-qPCR for PRRSV and negative for antibodies against PRRSV prior to the start of the study. As the wording 'primed' is frequently used in science but not common in the product literature for immunological veterinary products, the following proposed wording for 'seropositive sows' was accepted by the applicant: *'non-PRRS virus-naïve gilts and sows (i.e. either previously immunised against PRRS virus via vaccination or exposed to PRRS virus via field infection)'*.

Furthermore, the applicant proposes to **delete the wording 'The use is not recommended during lactation**' in SPC section 4.7., but to add the wording 'Use only according to a benefit/risk assessment by

the responsible veterinarian'. There was no study performed on the safety of the use of Suvaxyn PRRS MLV during lactation with the initial marketing approval dossier nor with any post-authorisation variation and this is fully reflected by the retained sentence 'The safety of the vaccine has not been established during lactation'. Thus, the deletion of the wording 'The use is not recommended during lactation' is supported. This deletion is also considered acceptable, as no studies were performed in sows vaccinated during lactation and therefore no information on shedding via milk or any other negative consequences is given. Furthermore, as the present variation proposes to extend the DOI in sows to 26 weeks, a re-vaccination during lactation is more unlikely in contrast to the current duration of immunity of 16 weeks. The applicant accepted not to add the wording 'Use only according to a benefit/risk assessment by the responsible veterinarian' as it is considered unnecessary.

# 3. Benefit-risk assessment of the proposed change

Suvaxyn PRRS MLV is a live vaccine authorised for the 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).

The proposed grouped variation is to:

- Reduce the OOI in pigs from 28 days to 21 days,
- Extend the DOI in gilts and sows to 26 weeks, thereby harmonising duration of immunity in all pigs to 26 weeks,
- Introduce an additional indication (reduction of body weight losses of piglets (born from vaccinated gilts/sows) at weaning) and
- Propose changes to the wording of the immunological status of gilts and sows at the time of vaccination and other changes to the product information (make editorial change on the use during lactation section, change booster administration in line with the proposed DOI, etc.).

## *3.1. Benefit assessment*

**Direct therapeutic benefit**

The proposed benefit of Suvaxyn PRRS MLV is its efficacy to a shortened onset of immunity (OOI) 21 days post vaccination, extended duration of immunity (DOI) of 26 weeks and a prolonged re-vaccination every 6 months, which was investigated by laboratory studies conducted in sows. Suvaxyn PRRS MLV, by conferring these changes, could provide a more rapid and long-lasting, respectively, means of inhibiting disease spread within and between herds.

A well-designed laboratory study conducted in accordance with GLP is provided to demonstrate that the product is efficacious in pigs already 21 days after vaccination. The OOI of 21 days is therefore sufficiently shown.

Two well-designed laboratory studies conducted in accordance with GLP were presented to demonstrate that the product is efficacious in sows six months after vaccination as well as after a single booster vaccination given approximately six months after the first vaccination followed by a challenge another 7 months later. Both studies provide further support for DOI of 26 weeks in gilts and sows and re-vaccination every 6 months.

A reduction of body weight loss in piglets born from vaccinated sows had been additionally presented in the studies on duration of immunity. As no further data could be provided to support the relevance of the short-lived reduction in weight loss to the overall performance at the time of slaughter, the proposed claim has been withdrawn.

**Additional benefits**

None.

## *3.2. Risk assessment*

**Quality**

The quality remains unaffected by this variation.

**Safety**

*Risks for the target animal:*

Risk for the target animals remains unaffected by this variation. The administration of Suvaxyn PRRS MLV (porcine respiratory and reproductive syndrome virus vaccine (live)) in accordance with SPC recommendations is generally well tolerated. Whilst the new studies presented were not safety studies, the adverse events observed were no worse than that described in the current SPC.

*Risk for the user:*

Risk for the user remains unaffected by this variation.

*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.

*Risk for the consumer:*

Risk for the consumer remains unaffected by this variation.

*Special risks:*

None.

## *3.3. Risk management or mitigation measures*

The proposed change should not impact on the user safety, environment safety and consumer safety of the product as authorised.

## *3.4. Evaluation of the benefit-risk balance*

The benefit-risk balance remains unchanged.

# 4. Conclusion

Based on the original and complementary data presented on safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of

the marketing authorisation for Suvaxyn PRRS MLV can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No 1234/2008), as follows:

- Reduction of the onset of immunity for fattening pigs and gilts and sows from 28 days to 21 days
- Extension of the duration of immunity for gilts and sows from 16 weeks to 26 weeks
- Following changes to the product information:
  - Change of the wording 'seronegative sows' to 'PRRS virus-naïve gilts and sows'
  - Change of the wording 'seropositive sows' to 'non-PRRS virus-naïve gilts and sows (i.e. either previously immunised against PRRS virus via vaccination or exposed to PRRS virus via field infection)'
  - Deletion of the wording 'The use is not recommended during lactation'

The following proposed change has been withdrawn by the applicant:

- Proposed claim of the 'reduction of body weight loss in piglets at weaning'

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

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

I and IIIB

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

As a consequence of these variations, sections 4.2, 4.3, 4.5, 4.6, 4.7, 4.9 and 4.10 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.