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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Suvaxyn CSF Marker (EMEA/V/C/002757/II/0009)

Vaccine common name: Classical swine fever vaccine (live, recombinant)

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 4 December 2020 an application for a type II variation for Suvaxyn CSF Marker.

1.2. Scope of the variation

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

To modify the approved therapeutic indication by adding the indication "For active immunisation of breeding females to prevent transplacental infection leading to the birth of persistently infected piglets". Additionally, the applicant proposes a number of changes to the SPC, including changes to the SPC text in section 4.4 Special warnings for each target species.

The MAH also took the opportunity to introduce some minor editorial changes to the product literature.

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

<u>Active immunisation of breeding females to reduce transplacental infection</u>

The applicant has proposed to add a new indication for the product, based on the submitted documentation in the **study** *"Protection against transplacental transmission of classical swine fever virus using live marker vaccine "CP7_E2alf".*

Updated indication proposed by the Applicant, highlighted in **bold**:

"**4.2 Indications for use, specifying the target species**

For active immunisation of pigs from 7 weeks of age onwards to prevent mortality and reduce infection and disease caused by classical swine fever virus (CSFV).

Onset of immunity: 14 days after vaccination

Duration of immunity: at least 6 months after vaccination

For active immunisation of breeding females to reduce transplacental infection caused by CSFV.

Onset of immunity: 21 days after vaccination

Duration of immunity has not been demonstrated.

In addition to the proposed new indication in section 4.2, the applicant has proposed a number of changes to the text of the SPC sections 4.4, 4.7, 4.9 and 5, and sections 4, 8, 12 of the PL."

The applicant has also proposed that the stated special warning in section 4.4 of the SPC be deleted. The section 4.4 of the SPC has been amended as follows:

"Protection against transplacental transmission of CSFV was shown 21 days after vaccination when challenge was applied in 6 pregnant sows with a moderately virulent CSFV strain. Partial protection against transplacental transmission of CSFV was observed when challenge was applied in 6 pregnant sows with a highly virulent CSFV strain.

Birth of persistently infected immunotolerant piglets represent a very high risk since they are shedding field virus and they cannot be identified serologically due to their seronegative status. Vaccination of breeding animals may be included in risk-based control strategies in case of outbreak and considering the above information."

At present, the SPC contains warnings against the vaccination of sows due to the lack of protection against vertical transmission after an early and highly virulent challenge presented in the original dossier, study *Protection of the CP7_E2alf vaccine administered by i.m. or oral route against transplacental infection in pregnant sows which are free from Pestivirus antibodies*. This study was assessed in connection with the submission at the time of the original application for marketing authorisation (EMEA/V/C/002757/0000). In the present application, no additional documentation has been provided concerning this specific study report, in which challenge inoculations took place 14 days after vaccination of pregnant sows. In the study, 10 pregnant sows (at 43-48 days of gestation), free of pestivirus antibodies, were vaccinated either orally (n=2) or intramuscularly (n=6) with a single dose of the Suvaxyn CSF Marker vaccine. Two additional sows were included as untreated controls. Fourteen days after vaccination (between 57th and 62nd day of gestation), all animals were challenged oronasally with the virulent CSFV challenge strain "Koslov".

The sows in the study were at the appropriate stage of gestation and could be considered as representative for the most sensitive animals that are proposed for vaccination. The vaccine was at the minimum titre and prepared using the virus strain at the most adapted passage level for efficient vaccination.

The challenge caused clinical signs and death of one of the control animals. The other control sow survived and was without clinical signs. Live CSF virus was isolated from the foetuses of the apparently unaffected sow so clearly transplacental transfer of the infection did take place. This indicated that the challenge was severe and valid according to the Ph. Eur. Monograph 0065: Swine fever vaccine (LIVE, prepared in tissue cultures) classical.

Virus was detected by RT-qPCR in serum samples from both control sows and in 4 of 6 intramuscularly vaccinated sows. The Ph. Eur. Monograph 0065 states: *"the vaccine complies with the test if no virus is found in the blood of vaccinated sows and in foetuses from the vaccinated sows, and no antibodies against classical swine fever virus are found in the serum of the foetuses from vaccinated sows"*. The challenge study results did not meet the efficacy criteria set in the monograph for classical live CSFV vaccines.

Some of the sows vaccinated by the intramuscular route developed some antibodies against CSFV E2 by 14 days after vaccination. There were no clinical signs in the vaccinated sows after CSFV challenge.

It is clear from the presented data that the vaccine was not sufficiently efficacious against transplacental transfer of virulent challenge infection, as the results showed substantial transmission from sows to foetuses. Data from RT-qPCR tests on foetal organ samples have not been presented from four of the six intramuscularly vaccinated sows. In addition, the presented results on efficacy do not comply with the criteria set out in the Ph. Eur. Monograph 0065, Swine fever vaccine (LIVE, prepared in tissue cultures) classical.

In addition, another experimental study was submitted- Protection against postnatal classical swine fever virus persistence in suckling pigs using Suvaxyn® CSF Marker and Pestiporc. The documentation presented in this study is not considered within the scope of the present application.

The applicant has presented a new study, *Protection against transplacental transmission of classical swine fever virus using live marker vaccine "CP7_E2alf",* where the chosen challenge was based on a strain of CSFV ('Roesrath') known for developing mildly virulent infections in sows.

The conditions were further adapted to set less stringent conditions, as the challenge exposure was administered 21 days post vaccination, which is 7 days later compared to the schedule for challenge exposure after vaccination stipulated in Ph. Eur. Monograph 0065 (Swine fever vaccine (LIVE, prepared in tissue cultures) classical). The latter study, (*Protection of the CP7_E2alf vaccine administered by i.m. or oral route against transplacental infection in pregnant sows which are free from Pestivirus antibodies)* employed the stringent criteria stipulated in Ph. Eur. Monograph 0065 (Swine fever vaccine (LIVE, prepared in tissue cultures) classical). The alternative less stringent schedule involving a 21-day interval between vaccination and challenge exposure of pregnant sows is outlined in the OIE Terrestrial Manual (2019), Chapter 3.8.3. Classical swine fever (infection with classical swine fever). This OIE guideline underlines that the presented minimum requirements for CSFV live vaccines cover use of the vaccines broadly in different epidemiological settings, and in endemic situations vaccination is mainly used to lower the impact of the disease or as a first step in an eradication program.

The new study (Protection against transplacental transmission of classical swine fever virus using live marker vaccine "CP7_E2alf"), comprises eight sows without antibodies against pestiviruses and reportedly all at day 44 of gestation at D0. The vaccine group (six sows) were vaccinated once with 1 dose of a vaccine batch. The batch was after vaccination determined by back-titration to a titre close to the minimum titre (the relevance of the back-titration result compared to the titre stated on the batch is not clear). The efficacy study report includes the relevant vaccine batch certificate. The two unvaccinated sows of the control group were housed separately from the vaccinated group (non-blinded). Three weeks after vaccination, reportedly on the 65th day of gestation, all eight sows were challenged oro-nasally with a dose of the CSFV challenge strain 'Roesrath' (CSF1045, 5 ml containing a titre of $10^{5.3}$ $TCID_{50}$/ml). This challenge was in general terms considered to kill at least 50% of non-vaccinated piglets in less than 21 days with reference to a publication around 2-3 years earlier (Petrov-et-al-2014). Before farrowing, the sows were killed, and their foetuses were examined for CSFV. Serum samples from sows and foetuses were tested for the presence of antibodies against CSFV. Isolation of CSFV was carried out from the blood of the sows (collected 7 and 9 days after challenge and at euthanasia), and from homogenised organ materials (tonsils, spleen, kidneys, lymph nodes) of the foetuses. In vaccinated sows and foetuses virus

infection was not demonstrated, indicating protection against transplacental transmission, while the two unvaccinated sows carried infected foetuses. The sows were killed before farrowing, and persistent infections in offspring of control sows have not been documented in any of the presented studies.

In conclusion, the sows in this study were at the 65th day of gestion at challenge, which is in line with the OIE Guideline Chapter 3.8.3. (2019) Classical swine fever (infection with classical swine fever) (challenge described between 55th to 70th days of gestation). In the previous study the sows were challenged 14 days after vaccination and between days 54 and 64 of gestation, which represents overall stricter conditions for proving protection against transplacental transmission of CSFV. The sows of the new study were at an appropriate sensitive stage of gestation when vaccination took place. The vaccine was considered representative of a minimum potency. The virus strain was at a representative passage level for efficient vaccination. The challenge exposure did not result in recognisable fever reactions in the sows. The mildly virulent infections of control sows were characterised by subclinical to mild clinical signs in sows on a single day post challenge (day 13 post challenge).

The design and results of the limited study presented here together with the results of the previous study (which had a set-up overall in compliance with Ph. Eur. Monograph 0065 (Swine fever vaccine (LIVE, prepared in tissue cultures) classical), raise concern for the proposed indication on "prevention of transplacental infection" based on the principle of evaluation against representative worst-case scenarios for evaluation of efficacy.

When considering the data *in toto* for the proposed indication on "prevention of transplacental infection", it is not considered that sufficient data have been provided concerning representative worst-case scenarios for introduction of CSFV infection into European swine herds.

The applicant has shown protection against transplacental transmission in the new study report when a challenge was applied 21 days post vaccination in a limited number of sows. However, the study results should be considered in the overall context of risk of transplacental transmission, considering among others the timing between vaccination and challenge infection and the virulence of the challenge strain, as shown in the previous challenge study, where insufficient protection against transplacental infection was found.

The new indication in section 4.2 is associated with the amended warnings in section 4.4 and 4.5 in the SPC.

In view of the limited documentation provided for this vaccine which supports that it is only to be used in an outbreak situation within restricted control zones, it is considered acceptable that a general indication on reduction of transplacental transmission is stated in section 4.2 of the SPC. Discussion has been provided on outbreak scenarios in EU where vaccination of breeding animals may be included in risk-based control strategies. The stated clear disadvantage is that the so-called moderate/low virulent strains are able to cause both pre- and postnatal persistence. These strains are not killing the sow and can induce the postnatal persistence phenomenon in young, unprotected piglets.

The additional indication ***"the associated birth of persistently infected pigs"*** proposed by the Applicant has been deleted from the proposed new indication, as data have not been presented to support such indication.

Importantly in the potential scenario of an outbreak with a moderate/low virulent strain, decision to vaccinate sows should be taken based on the actual outbreak case, associated control zones, and the fact that birth of persistently infected immunotolerant piglets represents a very high risk since they are shedding field virus and they cannot be identified serologically due to their seronegative status.

This risk has been highlighted by the following new wording added to the SPC section 4.4 '*Special warnings for each target species'*:

"***Protection against transplacental transmission of CSFV was shown 21 days after vaccination when challenge was applied in 6 pregnant sows with a moderately virulent, CSFV strain. Partial protection against transplacental transmission of CSFV was observed when challenge was applied in 6 pregnant sows with a highly virulent CSFV strain.***
Birth of persistently infected immunotolerant piglets represent a very high risk since they are shedding field virus and they cannot be identified serologically due to their seronegative status. Vaccination of breeding animals may be included in risk-based control strategies in case of outbreak and considering the above information."

A particular safety aspect on vaccination of pregnant animals is the possible transplacental spread of the vaccine virus to the foetus. As any level of systemic spread of virus could result in transplacental transmission even if at very low level, then it appears likely that transplacental transmission occurs.

Vaccine infection of different lymphoid tissues has been demonstrated by RT-PCR for at least 63 days in vaccinated animals, while data is not available on systematic investigations for vaccine virus transmission and replication in lymphoid tissues of foetuses. The applicant argues that the risk of transplacental infection and spread is negligible. A well-known hallmark of pestiviruses is their ability to cross the placenta and multiply in the foetus at some stages of the gestation (Recent review in: Viruses 2020, 12, 1181, Bielfeldt-Ohmann et al.). It is concluded that transplacental transmission of the vaccine strain may occur and the following warning has been added to the SPC, section 4.5**: "Transplacental transmission of the vaccine virus has not been detected in the limited studies performed but cannot be excluded"**.

The following proposed wording: *'Shedding of vaccine virus has however not been detected but cannot be excluded.'* (SPC, Section 4.5 Special precautions for use) has not been accepted.

The present application focuses on transplacental transmission and data on shedding has not been presented as a focus for this application.

In conclusion, the SPC has been amended according to the available documentation with the following indication in section 4.2 of the SPC:
"***For active immunisation of breeding females to reduce transplacental infection caused by CSFV."***

The indication proposed by the Applicant ***"the associated birth of persistently infected pigs"*** has been deleted from the section 4.2 of the SPC.

The following warning has been included in section 4.4 of the SPC:

"Protection against transplacental transmission of CSFV was shown 21 days after vaccination when challenge was applied in 6 pregnant sows with a moderately virulent, CSFV strain. Partial protection against transplacental transmission of CSFV was observed when challenge was applied in 6 pregnant sows with a highly virulent CSFV strain.

Birth of persistently infected immunotolerant piglets represent a very high risk since they are shedding field virus and they cannot be identified serologically due to their seronegative status. Vaccination of breeding animals may be included in risk-based control strategies in case of outbreak and considering the above information."

The following warning has been added to the SPC, section 4.5**: "Transplacental transmission of the vaccine virus has not been detected in the limited studies performed but cannot be excluded".**

The following wording proposed by the Applicant: ***'Shedding of vaccine virus has however not been detected but cannot be excluded'*** (SPC, Section 4.5 Special precautions for use), has been deleted.

In addition, a safety study of one dose and a safety study of overdose testing in pregnant animals were presented in the original dossier. The report of the first study concerned pregnant sows of different phases of gestation including 10 sows in the 1st phase of gestation, 12 sows in the 2nd phase and thirteen in the 3rd phase and 6 placebo vaccinated control sows. Reproductive parameters and reproduction abnormalities are considered to be investigated further, based on data when the vaccine is used in the field.

Local and systemic adverse events were investigated and palpable, injection site reactions were observed in sows in the safety study of one dose. The vaccine was also associated with transient (1 day) hyperthermia 4 hours post vaccination (+2.91°C for one day) in a case in a vaccinated sow in this study.

The SPC section 4.6 has been updated accordingly:

"In laboratory safety studies in pregnant animals, the following adverse reactions were observed:

A local and transient tissue reaction in the form of swelling of up to 5 mm in diameter at the injection site was very common and lasted for up to 1 day. A transient increase in body temperature of 2.9 °C was observed commonly 4 hours after vaccination. This resolved spontaneously within 1 day after vaccination.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))

- common (more than 1 but less than 10 animals in 100 animals treated)

- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)

- rare (more than 1 but less than 10 animals in 10,000 animals treated)

- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)".

The following wording has been added to the section 4.7: ***"The vaccine can be used in sows during pregnancy".***

The following wording **in bold** has been added to section 4.9 of the SPC:
"Basic vaccination
A single 1 ml dose should be administered intramuscularly to pigs from 7 weeks of age ***and breeding females."***

The following wording **in bold** has been added to section 5 of the SPC:
"Challenge studies were conducted with **the highly virulent reference strain CSFV** Koslov (genotype 1) **and the moderately virulent, Roesrath strain (genotype 2, Germany 2009)**."

3. Benefit-risk assessment of the proposed change

This product is authorised for the active immunisation of pigs from 7 weeks of age onwards to prevent mortality and reduce infection and disease caused by classical swine fever virus (CSFV). The active

substance is a live E2 gene-deleted bovine viral diarrhoea virus containing the CSFV E2 gene. This suspension for injection is given in the dose of 1 ml. The withdrawal period is zero days.

The proposed variation is to modify the approved therapeutic indication by adding the below:

For active immunisation of breeding females to reduce transplacental infection by CSFV.

Onset of immunity: 21 days after vaccination
Duration of immunity has not been demonstrated.

In addition to the proposed new indication of section 4.2, the applicant has proposed a number of changes to the text of the SPC sections 4.4, 4.7, 4.9 and 5, and sections 4, 8, 12 of the PL.

Furthermore, the MAH also took the opportunity to introduce some minor editorial changes to the product literature, one of which is not considered acceptable.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of Suvaxyn CSF Marker concerning its efficacy in the proposed additional indication for active immunisation of breeding females to reduce transplacental infection was documented in a new laboratory study.

This documentation has led to the new indication for the vaccine: For active immunisation of breeding females to reduce transplacental infection caused by CSFV, with an onset of immunity of 21 days after vaccination. A duration of immunity has not been demonstrated.

Additional benefits

Remain unaffected by this variation.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Concerns have been raised for documentation of safety associated with the proposed new indication for Suvaxyn CSF Marker in pregnant animals, which has not been addressed and justified specifically for this application. The SPC has been updated accordingly.
A statement has been added to the SPC section 4.5 providing the information that transplacental

transmission of the vaccine virus may occur.

Based on previous study reports on vaccination of pregnant animals and reported safety events herein text has been added to the section 4.6 of the SPC covering the findings on local and systemic adverse events (palpable injection site reactions of up 0.5 cm lasting for up to one day were observed in sows (safety study of one dose report), the vaccine was also associated with transient (1 day) hyperthermia 4 hours post vaccination (+2.91°C for one day) in one case in a vaccinated sow (safety study of one dose report).

Risk for the user:

Risk for user is considered unaffected by this variation.

Risk for the environment:

Overall, the risk to the environment is indicated to be minimal, and warnings in the SPC mitigate risks, and recommendations on post-marketing studies have been agreed upon, should the vaccine be used in the field for emergency vaccination in field outbreaks. The vaccine is only to be used under emergency mass vaccination situations in CSFV-naïve domestic herds in restricted control zones related to outbreak situations and by the intramuscular route. Additional information on results from post-marketing studies concerning reproductive parameters and potential reproduction abnormalities could become relevant.

Risk for the consumer:

Considered unaffected by the variation.

Zero days withdrawal period, "No MRL required".

Special risks:

Concerning vaccination of pregnant animals and risk of birth of immunotolerant persistently infected offspring:

A warning has been included in section 4.4 of the SPC:
"Protection against transplacental transmission of CSFV was shown 21 days after vaccination when challenge was applied in 6 pregnant sows with a moderately virulent CSFV strain. Partial protection against transplacental transmission of CSFV was observed when challenge was applied in 6 pregnant sows with a highly virulent CSFV strain.
Birth of persistently infected immunotolerant piglets represent a very high risk since they are shedding field virus and they cannot be identified serologically due to their seronegative status. Vaccination of breeding animals may be included in risk-based control strategies in case of outbreak and considering the above information."

The following warning has been included in section 4.5 of the SPC**: "***Transplacental transmission of the vaccine virus has not been detected in the limited studies performed but cannot be excluded.*"

3.3. Risk management or mitigation measures

Only to be used in an outbreak situation in herds within restricted control zones.

3.4. Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is deemed positive.

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

Additional information on results from post-marketing studies concerning reproductive parameters and potential reproduction abnormalities could become relevant.

The product presents an acceptable risk for users and the environment when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

4. Conclusion

Based on the original and complementary data presented on 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 CSF Marker can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), to add a new indication associated with new wordings on *special risks c*oncerning vaccination of pregnant animals and risk of birth of immunotolerant persistently infected offspring.

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.