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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ZULVAC SBV Type II variation (EMEA/V/C/002781/II/0002/G)

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

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) an application for a grouped type II variation for ZULVAC SBV.

On 12 July 2012 the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on "Minor-Use-Minor-Species" (MUMS) are applicable when assessing Schmallenberg in sheep. On 13 September 2012 the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on MUMS are applicable when assessing Schmallenberg in cattle.

1.1.1. Scope of the variation

Variations requested		**Type**
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Two type II variations to change the vaccination schedule from two doses to one dose in sheep, and to extend the duration of immunity (DOI) in cattle. Both variations affect the SPC and PI, and deal with clinical aspects.

Current	**Proposed**
Variation 1. One-dose vaccination schedule in sheep	
SPC section 4.2 and leaflet section 4. Sheep: For active immunisation of sheep from 3.5 months of age to prevent viraemia* associated with infection by Schmallenberg virus. Onset of immunity: 14 days after completion of the primary vaccination course. Duration of immunity: 7 months after completion of the primary vaccination course. **SPC section 4.9 and leaflet section 8.** Sheep: Subcutaneous use (in the axillar region behind the elbow). Primary vaccination: **- For sheep from 3.5 months of age: administer two doses of 1 ml, three weeks apart.** - For female sheep at breeding age: the primary	**SPC section 4.2 and leaflet section 4.** Sheep: For active immunisation of sheep from 3.5 months of age to **reduce** viraemia* associated with infection by Schmallenberg virus. Onset of immunity: **21 days** after completion of the primary vaccination course. Duration of immunity: **6 months** after completion of the primary vaccination course. **SPC section 4.9 and leaflet section 8.** Sheep: Subcutaneous use (in the axillar region behind the elbow). Primary vaccination: **- For sheep from 3.5 months of age: administer** one dose **of 1 ml.** - For female sheep at breeding age: **administer one dose** of 1 ml at least 14 days prior to breeding.

vaccination course consisting of two doses of 1 ml administered three weeks apart should be completed at least 14 days prior to breeding. Booster vaccination: - For non-breeding sheep: administer two doses of 1 ml three weeks apart, every 6 months. - For female breeding sheep: the booster vaccination course consisting of two doses of 1 ml administered three weeks apart should be completed at least 14 days prior to every breeding.	Booster vaccination: - For non-breeding sheep: administer **one dose** of 1 ml, every 6 months. - For female breeding sheep: **administer one dose** of 1 ml at least 14 days prior to every breeding.
Variation 2. Twelve month DOI in cattle	
SPC section 4.2 and leaflet section 4. Cattle Duration of immunity: 6 months after completion of the primary vaccination course. **SPC section 4.9 and leaflet section 8.** Cattle Booster vaccination: administer two doses of 2 ml three weeks apart, every six months.	**SPC section 4.2 and leaflet section 4.** Cattle Duration of immunity: **12 months** after completion of the primary vaccination course. **SPC section 4.9 and leaflet section 8.** Cattle Booster vaccination: administer two doses of 2 ml three weeks apart, every **twelve months**.

2. Scientific discussion

2.1. Assessment

2.1.1. Change the recommended vaccination schedule (primary and booster) from two doses to one dose in sheep

Zulvac SBV is an inactivated vaccine against Schmallenberg virus (SBV) disease for use in sheep and cattle. The vaccine was granted a centralised marketing authorisation in February 2015.

Currently, the vaccination schedule for use in sheep consists two doses given three weeks apart. The proposal to change the vaccination schedule to one-shot is based on the demand in the field of a vaccination schedule that can offer a more rapid protection of the vaccinated animal and reduce handling of the animals.

In order to support the efficacy of such revised vaccination schedule in sheep, the applicant has provided three laboratory efficacy studies:

1	Onset of immunity in lambs	Study number B845R-ES-13-008
2	Duration of immunity in lambs	Study number B844R-ES-14-019
3	Efficacy in pregnant ewes vaccinated prior to pregnancy	Study number B845R-ES-13-009

1) Study B845R-ES-13-008: Onset of immunity after administration of 1-shot of Zulvac SBV in lambs

Twenty (20) 3-month-old crossbred lambs (below the minimum age), SBV-seronegative by ELISA and negative to the presence of SBV genome by RT-qPCR were randomly allocated into two groups of ten lambs in the treatment group and ten in the unvaccinated control group. The treatment group was vaccinated at D0 with 1 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0) given by the SC route in the axillary area. All lambs were challenged 3 weeks (D21) after vaccination with 5 ml of challenge stock administered intravenously. Titrations were not performed before or after challenge but the virus present in the inoculum had been quantified previously (6.18 $\log_{10}$ genome copies/ml). Viraemia was monitored from D0 to D7 post-challenge using a validated RT-qPCR.

No clinical signs related to vaccination were observed during the study. However, during the challenge period, lambs in both experimental groups suffered from a respiratory process (coughing and nasal discharge) and were all treated with an anti-inflammatory product; some lambs also received antibiotic treatment. No information on the clinical signs registered in the individual animals has been included in the study report and it should have been provided for completeness. Nonetheless, the respiratory process affected both experimental groups and the treatment administered did not appear to have an impact on the study results. For this reason, the point will not be pursued any further. Hyperthermia was observed in one vaccinated lamb and three control lambs, no statistically significant differences was observed between groups.

All the control lambs were viraemic at some point between day 1 and day 7 after challenge. The peak of viraemia was observed at day 3 after challenge with a maximum mean viral load of 5.63 $\log_{10}$ genome copies/ml plasma. Viraemia was observed on 5 consecutive days after challenge with a maximum individual duration of 2-4 days. The pattern of viraemia and the maximum viral load in the control lambs were consistent to those observed in the studies submitted in support of the marketing authorisation for Zulvac SBV, thus confirming the validity of the challenge. In the vaccinated group, viraemia was not observed in any of the lambs after challenge (day 0 to day 7 after challenge).

Overall conclusions:

The administration of Zulvac SBV (at minimum potency) according to the proposed vaccination schedule (1-shot) to lambs of the minimum recommended age was able to prevent viraemia when the vaccinated animals were exposed to virulent SBV at 21 days after vaccination. An onset of immunity of 21 days is therefore demonstrated.

2) Study B844R-ES-14-019: Duration of immunity after administration of 1-shot of Zulvac SBV in lambs

Twenty-eight (28) 3-month-old crossbred lambs (below the minimum age), SBV-seronegative by ELISA and negative to the presence of SBV genome by RT-qPCR were randomly allocated into two groups of 14 lambs in the treatment group and 14 in the unvaccinated control group. The treatment group was vaccinated at D0 with 1 ml of ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml and RP=1.0) given by the SC route in the axillary area. Although this batch was not formulated with the minimum antigen content, its relative potency was minimum (RP=1), which is the most relevant parameter with regards to efficacy.

Due to a change in the study set up, only 10 lambs were left in each group and challenged 195 days after vaccination with 5 ml of challenge stock administered intravenously. The challenge strain is the same used in the studies presented in the original MA dossier. Titrations were not performed before or after challenge but the virus present in the inoculum had been quantified previously (6.3 $\log_{10}$ genome copies/ml). Viraemia was monitored from D0 to D7 post-challenge using a validated RT-qPCR.

No clinical signs related to vaccination were observed during the study. None of the vaccinated and control lambs presented clinical signs related to SBV infection. None of the lambs in either group presented a rectal temperature ≥40.5ºC after challenge. Although it is not specified in the study report, no apparent differences in rectal temperature were observed between groups.

Neutralising antibodies were detected in 100% of the vaccinated lambs 21 days after vaccination.

All the control lambs (100%) were viraemic at some point between day 1 and day 7 after challenge. The peak of viraemia was observed at day 3 post-challenge with a maximum mean viral load of 6.31 $\log_{10}$ genome copies/ml plasma. Viraemia was observed during a total of 7 days with individual viraemia lasting for 3-6 days. The pattern of viraemia and the maximum viral load in the control lambs were consistent to those observed in the studies submitted in support of the marketing authorisation for Zulvac SBV, confirming the validity of the challenge.

In the vaccinated group, three out of ten lambs (30%) were viraemic. Viraemia was first observed at 1-2 days after challenge and lasted for 2 days (2 lambs) or 4 days (1 lamb). In the rest of the lambs (70%) viraemia was not detected at any time point after challenge.

The proportion of viraemic animals in the vaccinated group (30%) was significantly lower than in the control animals (100%) (Chi-square test, two-tailed 95% power, 0.05 level of significance). Also, virus loads in the vaccinated lambs were significantly lower compared to the virus loads in the control lambs (Mann-Whitney U-test, 0.05 level of significance).

Overall conclusions:

The administration of Zulvac SBV (at minimum potency) according to the proposed vaccination schedule (1-shot) to lambs of the minimum recommended age was able to reduce viraemia when lambs were challenged 6 months after vaccination. The proposed duration of immunity of 6 months with an efficacy claim of reduction of viraemia caused by SBV infection is demonstrated by the results of this study.

As a consequence of the change in the vaccination schedule from two-shots to one-shot and the results of study B844R-ES-14-019 where only reduction (instead of prevention) of viraemia was achieved at duration of immunity (6 months), the efficacy claim in non-breeding sheep has been downgraded to “reduction of viraemia”. The ability to elicit an immune response able to prevent viraemia in the vaccinated animal is the most important feature sought in a vaccine against Schmallenberg disease virus since the absence of the virus in the blood stream will minimise the risk of transmission of the virus from infected to susceptible animals by the insect vector.

However, it should be noted that vaccination with one dose of Zulvac SBV stills offer a very high level of protection as vaccination significantly reduced the incidence of viraemia and virus loads as complete prevention of viraemia was achieved in 70% of the vaccinated sheep. Moreover, it has to be noted that the single-shot vaccination scheme also offered complete protection against viraemia at onset of immunity. It is also pointed out that one of the main aims for SBV vaccines is protection against transplacental infection when exposure to SBV occurs during pregnancy. This protection has been demonstrated using a single-shot vaccination scheme, so the efficacy claim in pregnant sheep is not impacted by the proposed change and remains the same. The single-shot vaccination schedule offers relevant advantages as it minimises handling of the animals (reducing stress thus improving animal welfare) and economic costs thus making vaccination more attractive to farmers which could result in better vaccination coverages.

3) Study B845R-ES-13-009: Immunogenicity study of one Schmallenberg virus inactivated vaccine in pregnant ewes

Study B845R-ES-13-009 was already presented and assessed during the original marketing authorisation procedure. For completeness, the applicant has included it again in the data package submitted for the present variation.

It is worth mentioning that study B845R-ES-13-009 was accepted as the pivotal study in support of the current efficacy claim in breeding sheep. Even though the vaccination schedule used in this study (1-shot) was not in accordance with schedule originally recommended for Zulvac SBV (two-shots), it was considered as a worst-case scenario for the demonstration of efficacy.

Since this study has been assessed and the results have been accepted during the original MA procedure, it is not considered necessary to include further comments here.

The change in the vaccination schedule has no impact on the indication in breeding sheep included in section 4.2 of the SPC that will remain unchanged. Section 4.9 of the SPC has been amended to reflect the change in the vaccination schedule. The changes are considered acceptable.

2.1.2. Change of the duration of immunity in cattle from 6 to 12 months

Currently, the duration of immunity in cattle is 6 months. There is a desire of a longer duration of immunity in cattle as such change will offer longer protection to vaccination animals and will reduce the number of injections required over time and hence reduced the risk of adverse reactions, handling, etc.

In order to support the extension of the duration of immunity to 12 months in cattle, the applicant has presented a new laboratory efficacy study.

Study B834R-ES-13-224: Duration of immunity (12 months) of Zulvac SBV in calves

Twenty-four (24) 3.5–4-month-old Friesian calves, seronegative to SBV by ELISA and negative to the presence of SBV genome by RT-qPCR were randomly allocated into two groups of 14 calves in the treatment group and ten in the unvaccinated control group. The treatment group was vaccinated at D0 and D21 with 2 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0) given by the IM route in the neck. All calves were challenged at D391 (12 months after the booster vaccination) with 5 ml of challenge stock administered intravenously. Titrations were not performed before or after challenge but the virus present in the inoculum had been quantified previously (6.18 log10 genome copies/ml). Viraemia was monitored from D0 to D7 post-challenge using a validated RT-qPCR.

Hyperthermia was observed in two control calves between days 2 and 4 after challenge. Differences in the rectal temperatures between the vaccinated and control calves at day 3 ($p=0.057$) and day 4 ($p=0.05$) post-challenge, although very close to statistical significance ($p<0.05$), cannot be regarded as statistically significant. Nonetheless, Zulvac SBV does not include any claim about reduction of hyperthermia after challenge, so this point will not be pursued any further.

All the control calves became viraemic at some point between day 1 and day 7 after challenge. The peak of viraemia was observed at day 4 after challenge with a maximum mean viral load of 6.59 log_{10} genome copies/ml plasma. Viraemia was observed during a total of 7 consecutive days whilst individual viraemia lasted for 4-6 days. The pattern of viraemia and the maximum viral load in the control calves is consistent to those observed in the studies presented in support of the marketing authorisation for Zulvac SBV and thus it is considered valid.

In the vaccinated group, viraemia was not observed in any of the calves (n=11, as two calves had been excluded prior to challenge and one calf had died in the course of the study) after challenge. Neutralising

antibodies were detected in 100% of the vaccinated calves between day 35 and 391 after booster vaccination. A progressive decline in the mean titres (45.3 to 2) was observed over time which is considered normal and further confirms the lack of exposure of the calves to SBV before challenge.

Overall conclusions:

The administration of Zulvac SBV (at minimum potency) according to the proposed vaccination schedule to calves of the minimum recommended age was able to prevent viraemia when the vaccinated calves were exposed to virulent SBV 12 months after completion of the primary vaccination course. The extension of the duration of the immunity in cattle to 12 months is supported.

No studies were presented at the time of initial registration in support of the efficacy of a booster vaccination. For this reason, the SPC indicates that, for booster vaccination, the primary vaccination should be administered at the end of the duration of immunity period.

2.2. Summary and conclusions

Variation I: Change in the vaccination schedule in sheep

In support of the change of the vaccination schedule of Zulvac SBV in sheep from two-shot schedule to one-shot schedule, data from two new laboratory challenge efficacy studies in sheep aimed at demonstrating respectively the onset and duration of immunity following vaccination according the new vaccination schedule have been provided. The studies were carried out in lambs below the minimum age using vaccine batches of minimum potency. Vaccinated and control lambs were challenged with a virulent SBV challenge strain according to a validated challenge model. The results of the studies showed that vaccination with Zulvac SBV (1 ml) prevented viraemia when the lambs were challenged 21 days after vaccination. An onset of immunity of 21 days is therefore demonstrated.

In the duration of immunity study, lambs were challenged approximately 6 months after vaccination. In this case, vaccination did not fully prevent viraemia as 30% of the vaccinated lambs became viraemic. Nevertheless, vaccination appeared to reduce significantly the percentage of viraemic animals as well as virus loads after challenge. Overall, the results of this study support the proposed indication which has been downgraded from prevention of viraemia to reduction of viraemia for 6 months.

In order to support the efficacy of the new vaccination schedule in breeding female sheep before pregnancy, a study has been submitted that was presented during the original MA procedure. This study was assessed and its results formed the basis of the acceptance of the current efficacy claim in breeding female sheep which will remain unchanged.

Overall, the data provided by the applicant in support of the change in the vaccination schedule in sheep, from two-shots to one-shot are considered satisfactory. The consequential change in the efficacy claim in non-breeding sheep, from prevention to reduction of viraemia, is not considered to have a significant impact on the overall benefit-risk balance of the vaccine which remains positive.

Variation II: Change in the duration of immunity in cattle

To support the change of duration of immunity from 6 to 12 months, a new study in cattle of the minimum age using a batch of vaccine of the minimum potency has been carried out. Naïve calves were vaccinated according to the recommended vaccination schedule whilst a group of calves were included as non-vaccinated controls. All calves were challenged 12 months after the completion of the primary vaccination course with virulent SBV. To assess the efficacy of the vaccine, vaccinated and control animals were monitored after challenge for the presence of viraemia. The results showed that all the control calves became viraemic after challenge whereas none of the vaccinated calves did. Vaccination with Zulvac SBV according to the recommended vaccination schedule was able to effectively protect

vaccinated calves against viraemia when the animals were exposed to virulent SBV 12 months after vaccination. Thus, the proposed extension of the duration of immunity in cattle to 12 months is fully supported.

In principle, it is not considered that the periodic safety update report (PSUR) cycle for ZULVAC SBV needs to be re-started at this stage.

3. Benefit-risk assessment

3.1. Benefit assessment

The main benefit of the change of the vaccination schedule in sheep is that, in practice, only one shot will be required to achieve the protection claimed in the SPC in comparison to the current two-shot schedule. This is of particular relevance for a vaccine like Zulvac SBV that is likely to be used under emergency/outbreak situations. The change will reduce the number of injections required, and hence the risk of adverse reactions, animal handling, user risks, associated costs etc.

The main benefit of the extension of the duration of the immunity to 12 months is that vaccinated cattle will be protected during a more extended period of time. In addition, the change will reduce the number of injections, and hence less risk of adverse reactions, animal handling, user risk, etc.

3.2. Risk assessment

The risk identified in connection to the change in the vaccination schedule in sheep is related to the consequential downgrade of the efficacy claim in non-breeding sheep, from prevention to reduction of viraemia. It appears that with the proposed vaccination schedule, some vaccinated sheep could still develop viraemia after exposure to SBV, more likely at the end of duration of immunity when it was shown that only 70% of the vaccinated sheep were fully protected against viraemia after experimental SBV challenge. However, the efficacy claim in pregnant sheep, one of the main targets for vaccination against SBV, is not affected by the change in the vaccination schedule.

No risk has been identified derived of the extension of the duration of immunity in cattle.

3.3. Evaluation of the benefit-risk balance

The proposed change in the vaccination schedule in sheep has the benefit of reducing the number of vaccinations required to achieve the protection claimed in the SPC which will positively impact on animal welfare as it will reduce animal handling thus reducing animal stress as well as other associated risks (e.g. user risk, risk of adverse reactions). Also, the economic costs of vaccination will be reduced (e.g. less handling, fewer vaccine doses). This is of particular interest in the context of the potential field use of Zulvac SBV (e.g. vaccination campaigns). The change in the efficacy claim in non-breeding sheep from prevention of viraemia to reduction of viraemia is not considered to significantly impact on the overall benefit-risk balance of the product which will remain positive. The change in the duration of immunity in cattle will have no impact on the benefit-risk balance of Zulvac SBV which will remain positive.

Overall, no change to the impact on the environment is envisaged.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

4.1. Changes to the community marketing authorisation

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

Annexes I and IIIB