11 December 2014
EMA/786089/2014
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ZULVAC SBV (EMEA/V/C/002781/0000)

Common name: Schmallenberg virus vaccine (inactivated)

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On 26 November 2013 the applicant Zoetis Belgium SA submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for ZULVAC SBV, through the centralised procedure, falling within Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the Committee for Medicinal Products for Veterinary Use (CVMP) on 13 July 2012 as the product contains a new active substance: Schmallenberg virus inactivated. The rapporteur appointed was A.-M. Brady and the co-rapporteur G. Kulcsár.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

The following indications were proposed:

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; duration of immunity: 7 months.

For active immunisation of cattle from 3.5 months of age to reduce viraemia associated with infection by Schmallenberg virus. Onset of immunity: 14 days; duration of immunity: 6 months.

For active immunisation of female sheep to reduce viraemia and transplacental infection associated with infection by Schmallenberg virus during the first trimester of pregnancy. Onset of immunity: 14 days; duration of immunity: 5 months after completion of the primary vaccination course.

ZULVAC SBV contains inactivated Schmallenberg virus strain BH80/11-4 as the active substance, and aluminium hydroxide and saponin as adjuvants. The proposed route of administration is subcutaneous in sheep and intramuscular in cattle. The recommended dose of ZULVAC SBV is 1 ml in sheep and 2 ml in cattle.

The vaccine is presented as a suspension for injection in a cardboard box containing 1 high density polyethylene (HDPE) vial containing 50 ml of product which is equivalent to 25 doses in cattle or 50 doses in sheep.

On 11 December 2014 the CVMP adopted an opinion and CVMP assessment report.

On 6 February 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for ZULVAC SBV.

MUMS status

The applicant requested minor use minor species (MUMS) classification for this procedure by the CVMP, and the Committee at their 13 September 2012 meeting confirmed that, where appropriate, the data requirements in the appropriate CVMP guidelines on "minor use minor species data requirements" would be applied when assessing the application. MUMS status was granted as the proposed indication was considered a minor use in cattle and sheep.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (DDPS) was provided. Based on the information provided, the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse event occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The manufacture of the antigen and the finished product, including all packaging, and batch release is carried out by Zoetis Manufacturing & Research Spain S.L., Spain. The site is routinely inspected by EU regulatory authorities and has been inspected within the last three years and a valid good manufacturing practice (GMP) certificate is available. No additional inspections specific to this vaccine are considered necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system (DDPS) and the GMP certification of the manufacturing site are considered in line with legal requirements.

Part 2 – Quality

Composition

ZULVAC SBV is an inactivated vaccine intended for the active immunisation of sheep and cattle against Schmallenberg virus (SBV) disease.

It contains inactivated SBV strain BH80/11-4 as active ingredient and aluminium hydroxide gel 3% and saponin as adjuvants. The amount of inactivated SBV contained in each dose of vaccine ranging from between $10^{6.2}$ and $10^{6.7}$ $TCID_{50}$/ml (pre-inactivation titre) is expressed in relative potency units with respect to a reference vaccine which was shown efficacious in the efficacy studies. The following excipients are included: thiomersal as preservative and saline solution (potassium dihydrogen phosphate, disodium phosphate dihydrate, potassium chloride, sodium chloride, and water for injections) for volume adjustment.

The pharmaceutical form is a suspension for injection.

Container

The final product is presented in 50 ml HDPE vials. Each bottle is closed with a 20 mm diameter chlorobutyl rubber stopper and sealed with an aluminium cap.

The HDPE vials comply with the requirements of European Pharmacopoeia (Ph. Eur.) monograph 3.1.5 and the rubber stoppers comply with the requirements of Ph. Eur. monograph 3.2.9.

Development pharmaceutics

The vaccine strain was isolated from bovine serum in Schmallenberg (Germany), where the first case of the disease (index case) occurred. To date, limited information on the variability of the SBV is available but it is generally accepted that SBV strains currently present throughout Europe are derived from the first outbreaks of disease in Germany and the Netherlands. Given the short period of time

since the first outbreaks in 2011, it is reasonable to consider the SBV strain included in ZULVAC SBV relevant to the European SBV epidemiological context. Genomic sequencing has revealed some differences among SBV strains but the implication of these mutations are not currently understood. Overall the vaccine strain is considered relevant for the indication of the vaccine.

The selected adjuvant is aluminium hydroxide and saponin. Thiomersal is used as a preservative as the vaccine is a multi-dose presentation for food-producing species, this is acceptable.

Method of manufacture

The vaccine is manufactured by standard process. The SBV strain is cultured on cells using Glasgow minimal essential medium (GMEM) as cell culture medium. The GMEM is used both at the cell growth stage and at the virus growth stage.

For the cell growth stage the medium is supplemented with gentamicin in order to minimise risks of contamination due to manual handling which is considered acceptable.

In contrast, the medium used during the virus growth phase is not supplemented with gentamicin. The working seed lot virus (WSV) prepared from the master seed lot virus (MSV) is passaged two times in cellsin order to obtain the final antigen.

After harvest, the virus is inactivated with binary ethylenimine (BEI); the inactivation kinetics has been satisfactorily validated with a maximum pre-inactivation titre of $10^{6.7}$ $TCID_{50}$/ml. Once the inactivation process is completed, the residual BEI is neutralised with sodium thiosulfate solution. After this stage, bulk antigen can be stored at 2 °C – 8 °C for a maximum of 12 months. Data to support the storage of the bulk antigen for this period of time have been presented and are acceptable.

The finished product is formulated using an antigen concentration between $10^{6.2}$ and $10^{6.7}$ $TCID_{50}$/ml, expressed as pre-inactivation titre. A minimum of two lots of SBV antigen will be used to formulate any lot of finished product. Filling of the vials is carried out to guarantee a final filling volume of from 51 ml to 53 ml.

The proposed batch size for the final bulk vaccine is between 200 l and 2,000 l and it is considered acceptable.

The preparation of the finished product has been described in the dossier with sufficient level of detail.

Control of starting materials

Active substance

Detailed specifications for all starting materials used to manufacture the vaccine (including information on their function, species origin and treatment before use) were provided.

It can be concluded that testing carried out on both master cell seed (MCS) and MSV are satisfactory and in line to the requirements of the Ph. Eur.

Absence of endogenous retrovirus was satisfactorily demonstrated.

A SBV isolate, provided by the Central Veterinary Institute (the Netherlands), was used for the preparation of the neutralising antiserum used for extraneous agent testing. Both the virus isolate and cells used in the propagation were satisfactorily tested for extraneous agents.

Excipients

Detailed information and certificates of analysis were provided for all starting materials listed in a Ph. Eur. demonstrating compliance to respective Ph. Eur. monographs.

Starting materials not listed in a pharmacopoeia were described in detail. Adequate information was provided on the BHK-21 cell line, bovine calf serum, Glasgow minimum essential medium, trypsin and saponin. The MCS has been satisfactorily tested for extraneous agents in compliance with the table of extraneous agents to be tested for in relation to the CVMP guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/105112/2011).

The excipients contained in the finished product are in compliance with the relevant Ph. Eur. monographs.

In-house preparation of media and solutions

All the media and solutions used for the production of the vaccine are satisfactory prepared. The conditions for sterilisation of solutions prepared in-house were shown to be in compliance with Ph. Eur. monograph 5.1.1.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The documentation provided for all the materials of animal origin demonstrated their compliance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products *(*EMA/410/01 rev.3) and Commission Directive 1999/104/EEC.

It is concluded that, the risk of transmitting transmissible spongiform encephalopathy (TSE) infectivity through the use of this vaccine is negligible.

Control tests during production

The following control tests were carried out during antigen production: virus titration, sterility, identity, inactivation, presence of thiosulphate, absence of pestiviruses, absence of Aujeszky's disease virus and absence of bluetongue virus. The methods and acceptance criteria have been described in sufficient detail. Adequate validation data have been provided for all the tests.

The results of the analysis of in-process control tests for three consecutive production antigen batches were provided demonstrating batch-to-batch consistency. However, these batches had not been manufactured fully in accordance to the intended manufacturing method as gentamicin was used during the virus growth stage. Results from two consecutive antigen production runs manufactured in full accordance to the manufacturing method described in the dossier were also provided. Results of all the in-process control tests for these batches met the required specifications thus supporting the consistency of the antigen production. These antigen batches were used to prepare two batches of finished product.

One of the vaccine batches prepared with an individual antigen lot failed the batch potency test at release, thus not supporting consistency of production. Further data demonstrated that consistency of production is guaranteed when at least two antigen batches are used to formulate any batch of finished product.

Control tests on the finished product

The following control tests on the finished product were performed: appearance, volume, identity and batch potency, identification and quantification of aluminium hydroxide, thiomersal content, sterility and pH. The quality control of the finished product is appropriate. The specifications proposed are representative of those seen in the consistency batches.

The batch potency test is a challenge against a reference vaccine conducted in a line of mutant laboratory mice lacking interferon α/β and interferon-γ receptors which make them especially sensitive to SBV infection. A correlation between prevention of mortality or prevention of clinical signs and ZULVAC SBV antigen content was demonstrated in this model. The CVMP recommends however investigations to continue for development of an in vitro potency test in line with 3Rs principles (replacement, reduction and refinement), recommending replacement of the current in vivo potency test by an in vitro test whenever possible. The potency of any new batch of ZULVAC SBV will always be tested against a reference vaccine in the potency test in mice. The efficacy of the current reference vaccine (formulated with the minimum antigen content of $10^{6.2}$ $TCID_{50}$/ml) has been fully demonstrated in sheep and in cattle both in onset and duration of immunity studies. The validation of the batch potency test showed that there is a dose-response between the amount of antigen included in the vaccine and the protection against mortality and clinical signs after SBV challenge seen in mice. The test was able to differentiate between vaccines with an antigen content of $10^{6.2}$ $TCID_{50}$/ml and $10^{5.9}$ $TCID_{50}$/ml (half the amount of the antigen dose) and was shown to be repeatable and reproducible in terms of the level of protection conferred by the reference vaccine and also the level of clinical signs observed in the control mice. The CVMP recommends however that further investigations shall take place on the dose-response effect in order to further underpin the robustness of the potency test.

In order to provide extra assurances that only efficacious batches will be put into the market, batches will only be released if they show a relative potency (RP) ≥ 1.0 with respect to the reference vaccine and if the percentage of protection observed in the mice vaccinated with the test vaccine is ≥ 75%.

Overall, it is considered that it can be reasonably guaranteed that only potent batches will be released into the market. Future reference vaccine lots will be tested against the same standard.

An acceptable justification for the absence of a test for the estimation of saponin in the finished product has been given however the CVMP considers that a test to quantify saponin in the finished product shall be developed for this vaccine.

Regarding interference validation of the sterility test showed that interference is overcome and the test fully complies with Ph. Eur. monograph 2.6.1.

Data from two batches of vaccine with a view to demonstrating batch-to-batch consistency were provided. These batches of finished product were manufactured with antigens produced according to the manufacturing method described in the dossier.

Therefore, production data from a total of seven batches of finished product were presented (six GMP batches and one research and development batch to support the consistency of production). All the batches that were manufactured at the minimum antigen input of $10^{6.2}$ $TCID_{50}$/ml using at least two different antigen batches (a total of five batches) passed the potency test at release. These data are supportive of the consistency of production when at least two antigen batches are used at blending. More than one batch of antigen will likely be required to formulate the vaccine given the size of the standard vaccine batch of ZULVAC SBV (1,000 litres). The method of production therefore states that any batch of vaccine will be formulated with at least two batches of antigen.

Overall, the above approach is accepted on the basis of the two following points: i) consistency of production is sufficiently demonstrated when at least two antigen batches are used at formulation and ii) the existence of a fully validated potency test.

Overall, consistency of production has been sufficiently demonstrated. However, most of the consistency data provided were from batches manufactured not in full accordance with the standard method of production (i.e. gentamicin used at both the cell and virus growth stages) and only data from one batch of finished product manufactured according to the description in the dossier are available. Although the deviation from the standard production method is considered to have no impact on consistency of production, the CVMP considers that data for a second batch of finished product manufactured according to the dossier shall be provided whenever the next commercial batch is manufactured.

Stability

Stability data for the first virus passage show that the storage is guaranteed for 12 months at < 60 °C. The bulk antigen has been demonstrated to be stable for storage period of 12 months at 2 °C to 8 °C.

Full stability data are available for one production scale vaccine batch showing that ZULVAC SBV is stable for 15 months of storage to 2 °C to 8 °C. This batch of vaccine was not fully manufactured according to the manufacturing method (use of gentamicin during the virus growth phase) but it is considered to be representative of the shelf life of the product. Satisfactory stability data for one batch of vaccine manufactured in full accordance to the dossier are available up to 3 months of storage. The CVMP has considered the submission of the final stability results for the above mentioned batch by November 2015 and provision of information of any-out-specification-result in the meantime as a condition to the marketing authorisation. In addition, data on the stability of the current reference vaccine have been presented indicating no decline in the level of protection conferred after 14 months of storage at 2 °C to 8 °C. Overall, it is considered that a shelf life of 12 months for ZULVAC SBV can be granted.

ZULVAC SBV is intended for immediate use. It is estimated that the administration of the vaccine to 50 sheep would take 1.5 hours (2 min/dose) and to 25 cattle would take 2 hours (5 min/dose). Based on these calculations, the statement "use immediately" included in the summary of product characteristics (SPC) for this product is considered adequate.

Data on the effectiveness of the antimicrobial preservative included (thiomersal) in ZULVAC SBV have been presented covering preservative effectiveness at release only. The criteria fulfilled are considered acceptable for a veterinary vaccine although effectiveness will need to be confirmed at the end of shelf life. The CVMP considers that data to support the efficacy of the antimicrobial preservative at the end of shelf life should be provided. This is considered acceptable.

Overall conclusions on quality

ZULVAC SBV is an inactivated viral vaccine presented as a solution in 50 ml HDPE vials closed with chlorobutyl rubber stoppers and sealed with an aluminium cap. Both HDPE vials and closures are in compliance with Ph. Eur.

The method of manufacture is well described with sufficient degree of detail. The same conditions used for the validation of the inactivation kinetics are applied during routine production which guarantees that the viral antigen is fully inactivated.

The starting materials are of adequate quality. The MSV and MCS have been shown free from extraneous agents.

The main risks concerning TSE are considered negligible.

Control tests carried out at various stages during vaccine production and on the final product are in general adequately described and have been satisfactorily validated. Sufficient guarantees have been given that the batch potency test is able to detect sub-potent batches thus ensuring that only efficacious batches of vaccine are released to the market. The CVMP recommended the applicant to continue investigations to replace the current in vivo batch potency test by an in vitro test in line with the 3Rs concept and to support the robustness of the batch potency test by investigate further dose-response effects when variability in the potency results of vaccine batches formulated in the range of antigen input proposed occur. Consistency of production has been demonstrated when at least two antigen batches are used to formulate any batch of finished product

Stability data have been provided for the bulk antigen which support the proposed storage period of 12 months at 2 °C to 8 °C. The proposed shelf life of 12 months at 2 °C to 8 °C for the finished product is considered acceptable based on the data available so far and providing that data on the stability of the on-going batch production (without gentamicin) are provided as a condition to the marketing authorisation.

In addition, the CVMP recommends that the following information is provided post-authorisation:

- data showing the dose-response effect to further underpin the robustness of the potency test.

Part 3 – Safety

Introduction

ZULVAC SBV is intended for intramuscular (IM) immunisation of cattle from 3.5 months of age to reduce viraemia associated with infection by SBV and for subcutaneous (SC) immunisation of sheep from 3.5 months of age to prevent viraemia associated with infection by SBV. In addition, vaccination of breeding sheep before pregnancy according to the recommended schedule results in reduction of viraemia and transplacental infection associated with infection by SBV during the first trimester of pregnancy.

Safety documentation

No good laboratory practice (GLP) statements were provided for the laboratory safety tests except for one study in cattle. Overall, this is considered acceptable given that the studies were carried out to an acceptable quality standard and that there are no specific concerns on how the studies were conducted and that the results were not compromised.

Data in support of the breeds of animals included in the safety and the efficacy studies have been presented and are considered acceptable.

Laboratory tests

In order to support the safety of ZULVAC SBV, four laboratory studies were presented.

Safety of the administration of one dose and of the repeated administration of one dose

The safety of the administration of one dose and of the repeated administration of one dose were addressed in the same study for each of the target species and are summarised together under this section. The following safety studies were performed in compliance with Ph. Eur. monograph 5.2.6 on evaluation of safety of veterinary vaccines and immunosera, the International Cooperation on

Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL44 on target animal safety for veterinary live and inactivated vaccines (July 2008) and Directive 2009/9/EC.

Safety of the administration of one dose and of repeated administration of one dose in lambs

The aim of this study is to investigate the safety of administration of one dose and the repeated administration of one dose of ZULVAC SBV at a maximum antigen concentration in lambs of minimum recommended age (3.5 months) when administered by the SC route.

Twenty (20) 3.5-month-old, SBV-seronegative, healthy naúve lambs were enrolled in this study. The animals were allocated randomly into two groups: vaccinated and controls. In the vaccinated group 10 lambs were vaccinated three times 2 weeks apart (day (D)0, D14, D28), with 1 ml of ZULVAC SBV (of $10^{6.7}$ $TCID_{50}$/ml pre-inactivation titre), by the SC route. In the control group, 10 lambs were inoculated by the SC route at the same time with 1 ml of phosphate-buffered saline (PBS). After vaccination, the lambs were monitored for the presence of systemic and local reactions and the body weight was monitored weekly. In case of reaction the injection sites were also examined microscopically after sacrifice.

No systemic reactions were observed. A transient increase in rectal temperature (< 1.5 °C) was observed during the first 24 hours after each vaccination. Local reactions at the injection sites consisted in diffuse swellings up to 8 cm in diameter that evolved into diffuse/nodular swellings of < 2 cm in diameter lasting up to 47 days. Microscopically, subcutaneous fibrosis and granulomas were the most relevant findings which are lesions commonly observed at vaccine injection sites. No significant differences in the weekly body weight increase between the vaccinated and control groups were observed.

It can be concluded that the administration of one dose and the repeated administration of one dose of ZULVAC SBV is safe in lambs of the minimum age (3.5 months) when administered by the SC route. The adverse reactions observed in this study are appropriately reflected in the SPC.

Safety of the administration of one dose and of repeated administration of one dose in calves

The aim of this study is to investigate the safety of administration of one dose and of one repeated dose of ZULVAC SBV at a maximum antigen concentration in calves of minimum recommended age (3.5 months) when administered by the IM route.

Nine (9) 3.5-month-old, SBV-seronegative, naúve healthy calves were enrolled in this study. All the calves were vaccinated three times 2 weeks apart (D0, D14, D29), with 2 ml of ZULVAC SBV (of $10^{6.7}$ $TCID_{50}$/ml pre-inactivation titre), by the IM route (1^{st} vaccination in the right neck muscles; 2^{nd} vaccination in the left neck muscles; 3^{rd} vaccination in a different area in the right neck muscles). After vaccination, the calves were monitored for the presence of systemic and local reactions. In case of reaction the injection sites were also examined microscopically after sacrifice.

After each administration of the three doses of vaccine, no systemic reactions were observed. A transient increase in the rectal temperature (<1.5 °C) was observed during the first 48 hours after each vaccination. Local reactions at the injection site consisted of small granules up to 0.7 cm in diameter that persisted for a maximum of 10 days and were classified microscopically as moderate to severe granulomatous myositis and fibrosis.

It can be concluded that the administration of one dose and the repeated administration of one dose of ZULVAC SBV is safe in calves of the minimum age (3.5 months) when administered by the IM route.

The adverse reactions such as the transient increase in temperature and the local reactions at the injection site observed in this study are appropriately reflected in the SPC.

Safety of one administration of an overdose

No applicable.

Examination of reproductive performance

Safety studies have been carried out in pregnant animals of each target species according to Ph. Eur. monograph 5.2.6 and VICH GL44 even if ZULVAC SBV is not intended for use in pregnant animals.

Safety of the administration of one dose and of repeated administration of one dose in pregnant sheep

Study on safety of the administration of one dose and of a repeated dose

The aim of the first study was to demonstrate the safety of the administration of one dose and of a repeated dose of ZULVAC SBV at a maximum antigen concentration to ewes at different stages of pregnancy (from 2.5 to 5 months).

Twenty-eight (28) SBV-seronegative and SBV negative by real-time polymerase chain reaction (RT-PCR), healthy pregnant crossbred ewes (2.5–5 months of gestation) were randomly allocated, depending on the stage of gestation, into four experimental groups (2 vaccinated and 2 control groups). Pregnant sheep in group 1 (n=9) and group 2 (n=10) were vaccinated twice 3 weeks apart by the SC route (1st vaccination in the right axillary area and 2nd vaccination in the left axillary area) with 1 ml of ZULVAC SBV ($10^{6.7}$ $TCID_{50}$/ml pre-inactivation titre). Pregnant sheep in group 3 (n=5) and group 4 (n=4) were inoculated following the same schedule and route of administration with 1 ml of PBS. In order to avoid the potential impact of animal handling on the evaluation of the reproductive performance, group 1 (vaccinated ewes) and group 3 (control group) were monitored for local and systemic reactions, including monitoring of rectal temperatures whilst group 2 (vaccinated ewes) and group 4 (control group) were monitored for reproductive parameters.

No systemic reaction was observed after any of the vaccinations. A slight transient increase in the rectal temperature (< 0.8 °C) was observed in the vaccinated sheep. Local reactions at the injection site were observed in all the animals after the first and second vaccination and consisted in diffuse swellings of up to 8 cm in diameter that appeared between 3 to 6 days after vaccination and persisted as small subcutaneous granules of < 0.5 cm in diameter for at least 97 days.

All pregnant ewes (100%), either in group 2 and 4, reached parturition. In the vaccinated group 2, 88% of the lambs were born healthy whilst one lamb was born weak and died few hours later. In the control group, 67% of the lambs were born healthy and one lamb was born dead due to *Mycoplasma* spp. infection. One pregnant sheep from group 1 (vaccinated group) aborted 19 days after vaccination. In absence of abnormalities or macroscopic lesions this abortion was attributed to the frequent manipulation and not linked to vaccination with ZULVAC SBV.

In conclusion, although the study was based on a limited number of animals, the results indicate that vaccination did not have an impact on the reproductive parameters.

Study on vaccination schedule impact on fertility or conception rate

A second study was carried out to demonstrate that vaccination with ZULVAC SBV following the vaccination schedule recommended in the SPC does not have any impact on fertility or conception rate of the vaccinated animals.

Thirty-six (36), SBV-seronegative, healthy non-pregnant crossbred ewes were randomly allocated into three experimental groups (2 vaccinated and 1 control group), composed of 12 animals each. Sheep in the 2 treatment groups were vaccinated twice, 3 weeks apart by the SC route with 1 ml of ZULVAC SBV of two different batches. Sheep in control group were left non-vaccinated. All sheep were bred by natural mating from one week after the second administration of the vaccine.

In the first experimental group ewes were vaccinated and revaccinated with ZULVAC SBV ($10^{6.7}$ $TCID_{50}$/ml). Eighty percent (80%) of the ewes became pregnant during the first two weeks after being comingling with the males. In the second experimental group ewes were vaccinated and revaccinated with ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml, RP=1.1). Sixty-three and half percent (63.5%) of the ewes became pregnant during the first three weeks after being comingling with the males, while 9.5% of the ewes became pregnant during the fifth week. Twenty seven percent (27%) of the ewes did not get pregnant. In the control group 54% of the unvaccinated ewes became pregnant during the first three weeks after being comingling with the males, while 9.5% of the unvaccinated ewes became pregnant during the fourth week and 9.5% during the sixth week after being in contact with the males. Twenty seven percent (27%) of the unvaccinated ewes did not become pregnant.

There were no apparent differences in the conception rate among the experimental groups. The conception rate was even higher in the group vaccinated with the vaccine containing the maximum antigen content.

In conclusion, the conception rate was higher in the group vaccinated with the vaccine containing the maximum antigen content which indicates that vaccination with ZULVAC SBV had no influence on the conception rate when the primary vaccination course is completed at least 14 days prior to breeding.

Safety of the repeated administration of one dose in pregnant cattle

The aim of this GLP-compliant study was to investigate the safety of the repeated administration of one dose of Zuvac SBV in pregnant cows at different stages of the gestation (before and after 4.5 months of gestation). Due to the applicant's decision to withdrawn safety claim in pregnant cattle the following study is presented in only summary.

Thirty-nine (39) healthy pregnant and non-pregnant cows were allocated, depending on the stage of gestation, into six experimental groups. Three treated groups (non-pregnant cows, pregnant cows at < 4.5 months of gestation and pregnant cows at > 4.5 months of gestation) were vaccinated by the IM route twice, two weeks apart with one dose (2 ml) of ZULVAC SBV whilst three control groups (non-pregnant cows, pregnant cows at < 4.5 months of gestation and pregnant cows at > 4.5 months of gestation) were inoculated following the same schedule and route of administration with 2 ml of placebo (PBS).

Serological analysis performed before first vaccination showed that 23 out of 39 (59%) cows were positive for antibodies against SBV and negative to the presence of SBV by RT-PCR. No systemic reactions were observed after any of the vaccinations. A slight transient increase in the rectal temperature (< 1.4 °C) was observed in some of the vaccinated cows during the first 24 hours after vaccination. Local reactions at the injection site were observed after the first and the second vaccination. The local reactions observed included palpable nodules of 0.2 to 1 cm in diameter, visible

hard swellings of up to 9 cm in length or palpable thickening of the skin up of up to 11 cm in diameter and resolved in a maximum of 22 days.

Non pregnant cows from vaccinated and control groups were inseminated. Two vaccinated cows aborted during the first half of the gestation (from 2 to 4.5 months pregnancy) but abortion was not linked to vaccination. With relation to cows the second half of the pregnancy (from 4.5 to 6 months), the average length of gestation was similar in both experimental groups. No abortions were observed during the second half of gestation. Two stillborn calves were observed in the vaccinated group but no link with vaccination was found.

In conclusion, the results of this study indicate that vaccination with ZULVAC SBV has no relevant impact on the reproductive performance of the pregnant cows.

The vaccine batch used in this study ($10^{6.4}$ $TCID_{50}$/ml and RP=1.0) is not relevant for the demonstration of safety since it is not of the maximum titre or potency to be contained in a production batch as required by Ph. Eur. monograph 5.2.6. The safety claim in pregnant cattle was finally withdrawn.

Examination of immunological functions

ZULVAC SBV is a conventional inactivated vaccine containing compounds with no known adverse effect on immunological function.

Special requirements for live vaccines

Not applicable.

Study of residues

Not required.

The active ingredient being a substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In addition the other components of the vaccine are either listed in table 1 of the annex of Commission Regulation No. 37/2010 or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this product.

The withdrawal period is set at zero days.

Interactions

No specific studies have been conducted and a statement to this effect is included in the SPC.

Field studies

No specific studies have been conducted in order to investigate the safety of ZULVAC SBV under field conditions which is in line with the CVMP Guideline on data requirements for immunological veterinary products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/123243/2006-Rev.2).

The absence of field safety studies for ZULVAC SBV can be accepted under the assumption that pharmacovigilance data will identify any issues in the field.

User safety

The applicant has provided a user safety risk assessment for the vaccine prepared in accordance with the CVMP guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006). Due to the nature of the different components of ZULVAC SBV, no specific risks have been identified. The SPC contains an appropriate standard warning.

The CVMP therefore concluded that the user safety for this product is acceptable when used as recommended in the SPC.

Environmental risk assessment

The applicant has provided a Phase I environmental risk assessment (ERA) in compliance with the CVMP Note for guidance on the environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95).

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. The product is an inactivated vaccine and the active ingredient is inactivated according to the regulatory requirements. Consequently any risk of presence of live virus in the vaccine and excretion into the environment is negligible. Since the Phase I assessment does not indicate any potential risk for the environment, no ecotoxicological study is justified.

Based on the data provided the ERA can stop at Phase I. ZULVAC SBV is not expected to pose a risk to the environment when used according to the SPC.

Environmental risk assessment for products containing or consisting of genetically modified organisms

Not applicable.

Overall conclusions on the safety documentation

The administration of one dose and the administration of one repeated dose of ZULVAC SBV by the recommended route to lambs and to calves of the minimum age (3.5 months) was investigated and it is safe. A very common adverse reaction is the transient increase in the rectal temperature (< 1.5 °C) observed during the 24–48 hours after each vaccination. Local reactions at the injection sites consisted in subcutaneous fibrosis and granulomas are also observed very commonly. The adverse reactions observed in this study are appropriately reflected in the SPC.

In a safety study in pregnant ewes at 2.5–5 months of gestation it was shown that vaccination with ZULVAC SBV did not have an impact on the reproductive parameters. A relevant statement has been included in section 4.7 of the SPC.

Overall, the laboratories studies show that the safety profile of ZULVAC SBV when used as recommended is satisfactory and no relevant safety risks have been identified.

Field trials have not been performed in line with the CVMP Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/123243/2006-Rev.2). In addition, pharmacovigilance data gathered post-authorisation will provide with safety data from the field.

No negative impact on the immune system is to be expected as ZULVAC SBV is a conventional inactivated vaccine containing conventional compounds with no known adverse effect on immunological function.

No specific studies have been conducted to investigate the interactions of ZULVAC SBV with other veterinary medicinal products and thus an appropriate warning is included in the SPC.

The risk to the user is considered low when used as recommended in the SPC. An appropriate standard warning is included in the SPC.

Based on the data provided the ERA can stop at Phase I. ZULVAC SBV is not expected to pose a risk to the environment when used according to the SPC.

Residue studies are not required. The withdrawal period is set at zero days.

Part 4 – Efficacy

Introduction and general requirements

ZULVAC SBV is intended for intramuscular (IM) immunisation of cattle from 3.5 months to reduce viraemia associated with infection by SBV and for subcutaneous (SC) immunisation of sheep from 3.5 months to prevent viraemia associated with infection by SBV. In addition, vaccination is intended for breeding sheep to reduce viraemia and transplacental infection associated with infection by SBV during the first trimester of pregnancy.

The laboratory studies presented are compliant to the Ph. Eur. monograph 0062 on vaccines for veterinary use.

Field trials have not been carried out as justified by that sufficient laboratory studies have been performed and this is in line with the MUMS status of ZULVAC SBV (EMA/CVMP/IWP/123243/2006-Rev.2).

The primary variable taken into account to determine vaccine efficacy of ZULVAC SBV, was the detection of viraemia in the post-challenge animals, detected by a validated RT-PCR. The absence of viraemia was defined in relation to the limit of detection of the technique. It has been satisfactorily demonstrated that the inoculation of a number of ribonucleic acid (RNA) copies equivalent to the limit of detection of the technique does not induce viraemia in the target species. From this result it would appear that the minimum infectious dose of SBV would be higher than the minimum level of detection of the RT-PCR. Following this rationale, it could be accepted that absence of viraemia determined by the validated RT-PCR would be supportive of a prevention of viraemia claim. The limit of detection of the RT-PCR will be clearly reflected in the SPC. Experimentally challenged animals were inoculated with enough amount of virus so that all control animals become viraemic after challenge. The challenge strains for cattle and sheep derive from the same original isolate (MSV), after subsequent passages in target species in order to obtain different strains from the original MSV. The standard challenge model for cattle and sheep consisted of the intravenous administration of 5 ml of plasma from viraemic cattle or sheep (challenge stock).

Laboratory trials

Onset of immunity

Onset of immunity of an inactivated Schmallenberg virus vaccine in sheep

The objective of this study was to evaluate the immunogenicity of ZULVAC SBV against viraemia induced by SBV challenge, when administered at the minimum potency/antigen content in lambs of 3 months of age (less than the minimum recommended age) by the SC route.

Twenty-four (24) 3-month-old crossbred lambs, SBV-seronegative by ELISA and negative to the presence of SBV genome by RT-PCR were randomly allocated into two groups of 12 lambs in the treatment group and 12 in the unvaccinated control group. According to the recommended vaccination scheme, the treatment group was vaccinated twice 3 weeks apart (D0 and D21) 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. Fourteen (14) days after revaccination (D35) all the lambs were challenged. On the same day blood samples were collected to determine the presence of SBV neutralising antibodies. From D0 until D7 post-challenge, challenged animals were monitored daily for clinical signs, rectal temperatures and for the evaluation of SBV viraemia by means of RT-PCR.

After challenge, no clinical signs were observed in any animal and no differences in rectal temperature were detected among vaccinated and control lambs. None of the lambs of the vaccinated group developed viraemia after challenge whereas all the control lambs did, except one. Neutralising antibodies were detected in all vaccinated lambs at D35 (2 weeks after 2nd vaccination).

In conclusion, this study demonstrates the efficacy of ZULVAC SBV when administered at the minimum potency/antigen content, in lambs of the minimum age following the recommended vaccination schedule. The results of this study support an efficacy claim of prevention of viraemia with an onset of immunity of 14 days after completion of the primary vaccination.

Immunogenicity study of a single use of an inactivated Schmallenberg virus vaccine in pregnant ewes

The objective of this study was to evaluate the immunogenicity of ZULVAC SBV against viraemia induced by SBV challenge when administered at the minimum potency/antigen content in one shot (1 ml) in pregnant ewes and their progeny (transplacental protection).

Twenty-two (22) non-pregnant crossbred sheep, SBV-seronegative by ELISA and negative to the presence of SBV genome by RT-PCR were randomly allocated into two groups of 13 ewes in the treatment group and 15 in the unvaccinated control group. Sheep in the treatment group were vaccinated (D0) with 1 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0) by the SC route in the axillary area. From seventeen (17) days after vaccination, sheep were mated by natural mating. At approximately 45–50 days of gestation, confirmed pregnant sheep were challenged intravenously. At challenge, blood samples were collected to determine the presence of SBV neutralising antibodies. From D0 until D6 post-challenge, challenged animals were monitored daily for clinical signs, rectal temperatures and for the evaluation of SBV viraemia by means of RT-PCR. Detection of SBV genome in amniotic fluids was performed at D5/D6 post-challenge (by amniocentesis). Animals were sacrificed at D25/26 post-infection and SBV detection in the placenta and foetal tissues was carried out by RT-PCR.

After challenge, no systemic reactions were observed in the vaccinated animals. There were no statistical significant differences in the rectal temperatures between vaccinated and control groups post-challenge. No other clinical signs were observed after challenge. After challenge, all the control animals developed viraemia. In the vaccinated ewes, viraemia was consistently detected in 3 out of

12 ewes (25%) whilst in 4 out 12 (33%) of the ewes SBV was detected only at one time point. Viraemia load was statistically significantly reduced from D2 to D5 post-challenge.

SBV genome was detected in samples only from 1 out of 12 vaccinated sheep and from the stomach content of the foetus and from the placentoma. In the control ewes, SBV was detected in the spleen (5 out of 9; 56%), amniotic fluid (3 out of 9; 33%) foetuses/tissue samples (8 out of 9; 89%). Neutralising antibodies were detected in 61.5% of the vaccinated ewes at the time of challenge.

In conclusion, vaccination with ZULVAC SBV did not affect fertility or conceptions rates of the vaccinated ewes. The results of the study support the claim of reduction in viraemia (virus load) and reduction of transplacental infection when pregnant ewes are exposed to SBV at 40–50 days of pregnancy.

In this study only one dose of 1 ml of ZULVAC SBV (minimum potency) was given 17 days before the start of breeding (differently from the vaccination scheme recommended). This can be considered as a worst-case scenario for the demonstration of efficacy in pregnant ewes as immune response is expected to be even higher after a booster dose three weeks later which is the recommended schedule for ZULVAC SBV.

Immunogenicity study of a single use of an inactivated Schmallenberg virus vaccine in pregnant ewes
(Supportive study only)

The objective of this study was to evaluate the immunogenicity of ZULVAC SBV against viraemia and transplacental infection caused by SBV infection. This study was not carried out with a batch of minimum potency/antigen content and therefore data can only be considered as supportive information.

Thirty-nine (39) non-pregnant crossbred sheep, SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 13 sheep in the treatment group and 15 in the unvaccinated control group. Sheep in the treatment group were vaccinated (D0) and revaccinated (D21) with 1 ml of ZULVAC SBV not of minimum potency/antigen content ($10^{6.4}$ $TCID_{50}$/ml and RP=1.1) by the SC route in the axillary area. Due to different issues, some animals were excluded from the study post-inclusion. Fourteen (14) days after revaccination (D35), mating was performed using natural mating. At approximately 45–50 days of gestation, confirmed pregnant sheep were challenged intravenously. At challenge, blood samples were collected to determine the presence of SBV neutralising antibodies. From D0 until D6 post-challenge, challenged animals were monitored daily for clinical signs, rectal temperatures and for the evaluation of SBV viraemia by means of RT-PCR. Detection of SBV genome in amniotic fluids was performed from D4 to D8 post-challenge (by amniocentesis). Detection of SBV genome in the foetal tissues was carried out at the end of the study (sacrifice was carried out at D60).

After challenge, no clinical signs were observed in any animal. Rectal temperatures in control animals were significantly higher than in vaccinated animals at D4 and D5 post-challenge. Only one out of all the vaccinated sheep (1/13; 0.7%) presented viraemia 2 days after challenge. All the control sheep, except one (14/15; 93%), developed viraemia after challenge. SBV genome was not detected in any of the samples taken from the vaccinated sheep or their progeny. In contrast, SBV was detected from the amniotic fluid samples of 5 out of 11 non-vaccinated sheep (45%) and from amniotic fluid from 3 non-vaccinated sheep (27%) collected between D4 to D8 post-challenge. In addition, SBV was detected in spleen samples collected in 5 out of 11 non-vaccinated sheep (45%) and in foetal tissues of 3 out of 11 (27%) non-vaccinated sheep. Neutralising antibodies were detected in all vaccinated ewes at challenge.

In conclusion, vaccination with ZULVAC SBV did not affect fertility or conceptions rates of the vaccinated ewes. In addition, vaccination reduced the frequency and viral loads in the vaccinated ewes compared to the control ewes. With regards to transplacental infection, the percentage of detection of SBV in amniotic fluids in the control group was much lower than that observed in the challenge group but this has been justified by the fact that pregnant ewes were challenged in an earlier stage of foetal development in an attempt to maximise the chances of observing foetal malformations. In consequence, no conclusion can be drawn from this study with regards the effect of vaccination on transplacental infection. Nevertheless, this study can only be considered as supportive information because the vaccine batch used was not a minimum potency batch.

Onset of immunity of an inactivated Schmallenberg virus vaccine in calves

The objective of this study was to determine the onset of immunity of ZULVAC SBV against viraemia induced by SBV challenge when administered at the minimum potency/antigen content in calves at 3.5 months of age by the IM route.

Thirty-nine (39) non-pregnant crossbred calves, SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 10 calves in the treatment group and 8 in the unvaccinated control group. According to the recommended vaccination scheme, calves in the treatment group were vaccinated (D0) and revaccinated (D21) with 2 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0) by the IM route in the neck muscles. Fourteen (14) days after revaccination (D35) all the calves were challenged intravenously. At D21 and D35 (challenge), blood samples were collected to determine the presence of SBV neutralising antibodies. Clinical signs and rectal temperatures were monitored from D35 until D42 (D0 to D7 post-challenge). Viraemia was determined from D35 to D42 (D0 to D7 post-challenge).

No systemic reactions were observed after vaccination and before challenge. After challenge, two calves from the control group developed an anaphylactic shock and one of them was found dead the following date. The occurrence of anaphylactic shock is thought to be attributable to the nature of the challenge stock (calf plasma). Vaccinated calves did not show hyperthermia after challenge. One control calf was hyperthermic at D2 and D3 post-challenge. Rectal temperatures in control animals were significantly higher than in vaccinated animals at D5 after challenge. None of the calves of the vaccinated group developed viraemia after challenge (D0 to D7 post-challenge) whereas viraemia was detected in all the control calves. The peak of viraemia was observed at D3 post-challenge. Low levels of neutralising antibodies were detected in 6 out of 10 vaccinated calves (60%) at D21 (3 weeks after 1st vaccination) and increased markedly at D35 (2 weeks after second vaccination).

In conclusion, this study is fully supportive of the efficacy of ZULVAC SBV in calves of the minimum age following the recommended vaccination schedule. The efficacy claim supported by this study is "prevention of viraemia". Onset of immunity of 14 days after completion of the primary vaccination course is demonstrated.

Immunogenicity study of an inactivated Schmallenberg virus vaccine in calves

The objective of this study was to evaluate the efficacy of ZULVAC SBV against viraemia induced by SBV challenge when administered in calves at 3.5 months of age by the IM route. This study was not carried out with a batch of minimum potency/antigen content and therefore data can only be considered as supportive information.

Eighteen (18) healthy 3 to 4-month-old crossbred calves (of the minimum recommended age), SBV-seronegative by ELISA were randomly allocated into two different groups of 10 calves in the treatment group and 8 in the unvaccinated control group. According to the recommended vaccination scheme,

calves in the treatment group were vaccinated (D0) and revaccinated (D21) with 2 ml of ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml and RP=1.1) by the IM route in the neck muscles. Fourteen (14) days after revaccination (D35) all the calves were challenged intravenously with 20 ml of virulent plasma. At D35 (challenge) and D42, blood samples were collected to determine the presence of SBV neutralising antibodies. Clinical signs and rectal temperatures were monitored from D35 until D42 (D0 to D7 post-challenge). Blood samples were collected at D35 and from D38 until D42 (D3 to D7 post-challenge) for the evaluation of SBV viraemia.

After challenge, no general clinical signs were observed in any of the animals after challenge. Rectal temperatures in control animals were significantly higher than in vaccinated animals at D2, D4 and D5 after challenge. None of the calves of the vaccinated group developed viraemia after challenge (D3 to D7 post-challenge) whereas all the control calves did. The peak of viraemia was observed at D4 post-challenge. Neutralising antibodies were detected in all vaccinated calves at D35 (2 weeks after 2nd vaccination).

In conclusion, this study would demonstrate the efficacy of ZULVAC SBV (using a vaccine batch containing more than the minimum antigen content/potency) in calves of the minimum age following the recommended vaccination schedule. The efficacy claim that could be supported would be "prevention of viraemia". Challenge of the calves was carried out 14 days after the second vaccination, thus an onset of immunity of 14 days after completion of the primary vaccination course would be supported. Although viraemia was not monitored during D1 and D2 after challenge, the peak of the viraemia in the control animals occurred at D4 after challenge, and this would be the worst-case scenario for demonstration of vaccine efficacy. Nevertheless, this study can only be considered as supportive information because the vaccine batch used was not a minimum potency batch.

The influence of maternal antibody on the efficacy of the vaccine

The efficacy of the vaccine in relation to maternally derived antibodies (MDA) has not been investigated. A warning has been included in the relevant section (4.4) of SPC.

No suitable data have been provided to support the efficacy of ZULVAC SBV in seropositive animals having antibody levels representative of those commonly found in the field (in an area of previous exposure to SBV).

Duration of immunity

Duration of immunity of an inactivated Schmallenberg virus vaccine in lambs (7 months)

The objective of this study was to determine the duration of immunity of ZULVAC SBV against SBV challenge when administered at the minimum potency/antigen content in 3-month-old lambs when challenged 7 months after vaccination.

Twenty-six (26) 3-month-old crossbred lambs (less than the minimum recommended age), SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 15 lambs in the treatment group and 11 in the unvaccinated control group. According to the recommended vaccination scheme, lambs in the treatment group were vaccinated (D0) and revaccinated (D21) with 1 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0) administered by the SC route in the axillary area. Blood samples were collected at D36, D65, D96, D124, D159 and D197 for the detection of SBV neutralising antibodies. All the lambs were challenged 232 days (approximately 7 months) after the completion of the primary vaccination course (D237) with 5 ml of virulent plasma given intravenously. Clinical signs and rectal temperatures were monitored from D0 until D7 post-

challenge. Blood samples were collected from D0 to D7 post-challenge for the evaluation of SBV viraemia and SBV neutralising antibodies.

No systemic reaction was observed after the first or second vaccination in any of the vaccinated lambs. After challenge, clinical signs were observed in two control lambs on D5–7 post-challenge. One lamb showed increased rectal temperature at D5 post-challenge and was found dead one day later. No specific lesions were found in the necropsy. None of the vaccinated lambs showed a rectal temperature ≥ 40.5 °C after challenge whilst one control lamb showed a rectal temperature ≥ 40.5 °C on D1 post-challenge. No significant increase in the rectal temperatures was recorded in the control lambs after challenge. None of the lambs of the vaccinated group developed viraemia after challenge (D0 to D7 post-challenge) whereas the SBV genome was detected in all the control lambs. Neutralising antibodies were detected in all vaccinated lambs from two weeks after second vaccination (D36) and declined progressively until the day of challenge. Control lambs remained SBV-seronegative during all the vaccination period.

In conclusion, this study is supportive of 7-month duration of immunity with an efficacy claim of prevention of viraemia when ZULVAC SBV used at minimum potency/antigen content is administered to lambs of minimum age according to the recommended vaccination schedule.

Duration of immunity of an inactivated Schmallenberg virus vaccine in lambs (Supportive study only)

The objective of this study was to determine the duration of immunity of ZULVAC SBV against SBV challenge in 3-month-old lambs, when challenged 7 months after vaccination. This study was not carried out with a batch of minimum potency/antigen content and therefore, the data can only be considered as supportive information.

Thirty-two (32) 3-month-old crossbred lambs (less than the minimum recommended age), SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 18 lambs in the treatment group and 14 in the unvaccinated control group. According to the recommended vaccination scheme, lambs in the treatment group were vaccinated (D0) and revaccinated (D21) with 1 ml of ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml and RP=1.1), administered by the SC route in the axillary area. Blood samples were collected at D55, D98, D139, D202, D228 for the detection of SBV neutralising antibodies. All the lambs were challenged 216 days (approximately 7 months) after the completion of the primary vaccination course (D237) with 5 ml of virulent plasma given intravenously. Clinical signs and rectal temperatures were monitored from D0 until D7 post-challenge. Blood samples were collected from D0 to D7 post-challenge for the evaluation of SBV viraemia.

No systemic reaction was observed after the first or second vaccination in any of the vaccinated lambs. After challenge, no clinical signs were observed in any of animals during the experimental period. No significant increase in the rectal temperatures was recorded in the control lambs after challenge. None of the lambs of the vaccinated group developed viraemia after challenge (D0 to D7 post-challenge) whereas the SBV genome was detected in all the control lambs. Neutralising antibodies were detected in all vaccinated lambs at D55 (5 weeks after 2nd vaccination). Control lambs remained SBV-seronegative during all the vaccination period.

In conclusion, this study was not carried out using a batch of vaccine of the minimum potency/antigen content and therefore, it cannot be considered relevant to support the duration of immunity of ZULVAC SBV in lambs. In addition, there are some reserves regarding the potential exposure of the animals to SBV challenge since the level of neutralising antibodies increased markedly before challenge (between D139 and D202).

Duration of immunity of an inactivated Schmallenberg virus vaccine in calves (6 months)

The objective of this study was to determine the duration of immunity of ZULVAC SBV, against SBV challenge when administered at the minimum potency/antigen content when administered in calves at 3 months of age by the IM route evaluated by challenge at 6 months after primary vaccination schedule.

Twenty-six (26) 3-month-old crossbred calves (less than the minimum recommended age), SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 14 calves in the treatment group and 12 in the unvaccinated control group. According to the recommended vaccination scheme, calves in the treatment group were vaccinated (D0) and revaccinated (D21) with 2 ml of ZULVAC SBV ($10^{6.2}$ $TCID_{50}$/ml and RP=1.0), administered by the IM route in the neck muscles. Blood samples were collected at D35, D52, D85, D113, D141, D174 and D203 for the detection of SBV neutralising antibodies. All the calves were challenged approximately 6 months after the completion of the primary vaccination course (D203) with 5 ml of virulent plasma given intravenously. Clinical signs and rectal temperatures were monitored from D0 until D7 post-challenge. Blood samples were collected from D0 to D7 post-challenge for the evaluation of SBV viraemia. Neutralising antibodies were also determined 7 days after challenge.

Three calves from the vaccinated group were found dead on D26, D45 and D55 but it was not related to vaccination. After challenge, no clinical signs were observed in any of animals. Rectal temperatures after challenge were always below 40 °C in both the vaccinated and non-vaccinated calves. The temperatures were significantly higher in the control calves in comparison to vaccinated calves at D2 post-challenge. All control calves developed viraemia between D1 to D2 after challenge. None of the calves of the vaccinated group developed viraemia after challenge (D0 to D7 post-challenge). Neutralising antibodies were detected in all vaccinated calves at D35 (2 weeks after 2nd vaccination). Control calves remained SBV-seronegative during all the vaccination period. The level of neutralising antibodies decreased from D35 to D203, before challenge.

In conclusion, this study is supportive of duration of immunity of 6 months with an efficacy claim of prevention of viraemia, in calves of the minimum recommended age vaccinated according to the recommended schedule with a batch of vaccine of the minimum potency.

Duration of immunity of an inactivated Schmallenberg virus vaccine in calves (Supportive study only)

The objective of this study was to determine the duration of immunity of ZULVAC SBV against SBV challenge in 2.5 to 3-month-old calves, when challenged 6 months after vaccination. The vaccine batch used in this study is not of the minimum potency/antigen content to be contained in ZULVAC SBV therefore it can only be considered as supportive data.
Twenty-two (22) 2.5 to 3-month-old crossbred calves (less than the minimum recommended age), SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 12 calves in the treatment group and 10 in the unvaccinated control group. According to the recommended vaccination scheme, calves in the treatment group were vaccinated (D0) and revaccinated (D21) with 2 ml of ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml and RP=1.1), administered by the IM route in the neck muscles. Blood samples were collected at D55, D98, D139, D167 and D202 for the detection of SBV neutralising antibodies. All the calves were challenged 189 days (approximately 6 months) after the completion of the primary vaccination course (D210) with 5 ml of virulent plasma given intravenously. Clinical signs and rectal temperatures were monitored from D0 until D7 post-challenge. Blood samples were collected from D0 to D7 post-challenge for the evaluation of SBV viraemia.

No systemic reaction was observed after the first or second vaccination in any of the vaccinated calves. After challenge, no clinical signs were observed in any of animals during the experimental period except for one calf that died due to anaphylactic shock just after challenge. Rectal temperatures after challenge were below 40 °C in the vaccinated calves whilst hyperthermia was observed in 3 of the control calves. The temperatures were significantly higher in the control calves in comparison to vaccinated animals at D2 and D4 post-challenge. Viraemia was detected in three of the vaccinated calves and in all the calves of the control group. The peak of viraemia in the control group was observed at D213. Neutralising antibodies were detected in 92% of the vaccinated calves at D55 (5 weeks after 2nd vaccination). Control calves remained SBV-seronegative during all the vaccination period. The level of neutralising antibodies decreased from D55 to D98 and then fluctuated around these levels at the rest of time points before challenge.

In conclusion, the study would be supportive of a claim of reduction of viraemia.

Response to booster of an inactivated Schmallenberg virus vaccine in calves

The objective of this study was to determine the efficacy of a booster vaccination with ZULVAC SBV against SBV challenge in 2.5 to 3-month-old calves when the booster vaccination is administered 7 months after the primary vaccination course and challenged is performed 6 months after booster vaccination.

Twenty-two (22) 2.5 to 3-month-old Friesian calves (except four crossbred calves), SBV-seronegative by ELISA and SBV negative by RT-PCR were randomly allocated into two different groups of 12 calves in the treatment group and 10 in the unvaccinated control group. According to the recommended vaccination scheme, calves in the treatment group were vaccinated (D0) and revaccinated (D21) with 2 ml of ZULVAC SBV ($10^{6.4}$ $TCID_{50}$/ml and RP=1.1) by the IM route. A booster vaccination with 2 ml of the same vaccine batch was administered to animals in the treatment group on D244 (7.4 months) after completion of the primary vaccination course. Blood samples were collected at D55, D98, D139, D167, D202, D229, D265, D291, D356 and D384 for the detection of SBV neutralising antibodies by ELISA. All the calves were challenged intravenously with 5 ml of plasma containing virulent SBV between D416 and D434 of the study (approximately 5.7-6.3 months after booster). Clinical signs and rectal temperatures were monitored from D0 until D7 post-challenge. Blood samples were collected from D0 to D7 post-challenge for the evaluation of SBV viraemia by RT-PCR.

No systemic reaction attributable to the vaccination was observed in any of the vaccinated calves. After challenge, no clinical signs were observed in any of animals during the experimental period except for one calf that showed signs of anaphylactic shock just after challenge, was treated and recovered 1 hour thereafter. Rectal temperatures after challenge were below 40 °C. Statistically significant differences were not observed between vaccinated and control animals. Viraemia was not detected in any of the animals before vaccination. After challenge, all control calves were viraemic except one at D1 post-challenge and remained viraemic until D5-D7 post-challenge. In the vaccinated animals, viraemia was detected in 5 out 7 of the vaccinated calves at several time points from D4 to D7 post-challenge. Neutralising antibodies were detected in all vaccinated calves except one at D55 (5 weeks after 2nd vaccination) and in all of them at D98. The level of neutralising antibodies decreased from D55 to D139 and increased again at D167 to decrease progressively until the day of challenge. Control calves remained SBV-seronegative during all the vaccination period.

In conclusion, this study is not considered relevant to support efficacy of a booster vaccination of ZULVAC SBV in cattle since the batch of vaccine used was neither of the minimum antigen content to be used at formulation ($10^{6.2}$ $TCID_{50}$/ml) nor of the minimum potency (RP=1.0). In the absence of suitable study to demonstrate the efficacy of a booster vaccination, the primary vaccination course will need to be repeated as booster vaccination.

Additional studies

No additional studies were presented.

Noting that SBV is not considered to be an emergency issue and that this application is not an exceptional circumstances, the inclusion of a statement in section 4.4 of the SPC regarding use of ZULVAC SBV in ruminant species other than cattle and sheep was not considered appropriate.

Compatibility

No data have been generated on the compatibility of ZULVAC SBV with any other veterinary medicinal product. A statement is included in section 4.8 of the SPC.

Field trials

No specific studies have been conducted in order to investigate the efficacy of ZULVAC SBV under field conditions since the efficacy of the vaccine has been appropriately addressed under laboratory conditions. This is in line with the CVMP Guideline on data requirements for immunological veterinary products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/123243/2006-Rev.2).

In conclusion, justification for the absence of field efficacy studies for ZULVAC SBV can be accepted, in consideration of the results obtained in the laboratory studies and also noting that pharmacovigilance data would provide safety information after use of the product in the field.

Overall conclusion on efficacy

The efficacy of ZULVAC SBV has been demonstrated under laboratory conditions using a vaccination-challenge model which is considered acceptable considering that this is an application classified as MUMS. The challenge strain is considered relevant for the demonstration of vaccine efficacy and also the route of administration of the challenge inoculum.

In sheep, laboratory trials are fully supportive of the following claim:

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.

In addition, the following additional efficacy claim in breeding sheep is also supported:

Vaccination of breeding sheep before pregnancy according to the recommended schedule described in section 4.9 of the SPC results in reduction of viraemia and transplacental infection associated with infection by Schmallenberg virus during the first trimester of pregnancy.

In order to protect from viraemia during pregnancy in sheep, the primary vaccination course should be given at least 14 days prior to breeding. No data have been presented in support of a booster vaccination in sheep which means that the primary vaccination will need to be repeated every 6 months.

In cattle, laboratory trials are fully supportive of the following claim:

For active immunisation of cattle from 3.5 months of age to reduce viraemia associated with infection by Schmallenberg virus.

Onset of immunity: 14 days after completion of the primary vaccination course.

Duration of immunity: 6 months after completion of the primary vaccination course.

The efficacy of the reference vaccine, formulated at $10^{6.2}$ $TCID_{50}$/ml (expressed as pre-inactivation titre) and with a relative potency=1.0, has been fully validated in both target species. Consequently, these specifications should be established as the minimum specifications required ensuring efficacy.

Clinical signs and rectal temperatures monitored during the efficacy laboratory studies showed that both in calves and lambs of the minimum recommended age, no local or systemic reactions occurred after vaccination with ZULVAC SBV. Moreover, clinical observation in vaccinated pregnant ewes showed that no systemic reactions were observed in the vaccinated animals.

No information is available on the efficacy of the vaccine when used in seropositive animals including those with maternally derived antibodies (MDA) and this is reflected in a statement included in SPC.

Part 5 – Benefit-risk assessment

Introduction

ZULVAC SBV is an inactivated vaccine containing SBV as the active ingredient and aluminium hydroxide and saponin as adjuvants. It is proposed for active immunisation of cattle and sheep to respectively reduce or prevent viraemia associated with infection by SBV and to reduce viraemia and transplacental infection associated with SBV in sheep during the first trimester of pregnancy. The product contains a new active substance (inactivated Schmallenberg virus).

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC.

The application has been classified as MUMS and therefore reduced data requirements have been considered in the assessment.

At present, there are no other Schmallenberg vaccines centrally authorised in the EU, although ZULVAC SBV and some other Schmallenberg vaccines have been granted provisional forms of authorisation at a national level.

Benefit assessment

Direct therapeutic benefit

In well conducted laboratory studies, ZULVAC SBV was shown to induce active immunisation in cattle from 3.5 months of age and to reduce viraemia associated with infection by Schmallenberg virus.

The product was shown to have an onset of immunity of 2 weeks (14 days) after completion of the primary vaccination course, which was demonstrated in 3.5 months old calves, and duration of immunity of 6 months after completion of the primary vaccination course.

ZULVAC SBV was also shown to induce active immunisation in sheep from 3.5 months of age and to prevent viraemia associated with infection by Schmallenberg virus.

The product was shown to have an onset of immunity of 2 weeks (14 days) after completion of the primary vaccination course, which was demonstrated in 3 months old lambs, and duration of immunity of 7 months after completion of the primary vaccination course.

Breeding sheep should be vaccinated before pregnancy according to the recommended schedule to reduce viraemia and transplacental infection associated with infection by SBV during the first trimester of pregnancy.

Additional benefits

ZULVAC SBV has been shown to reduce or prevent viraemia associated with Schmallenberg virus thus reducing the presence of the virus in the blood stream and hence the likelihood of transmission of the virus from an infected animal to the vector and consequently, the transmission of the virus to other susceptible animals.

The product provides a new treatment possibility against Schmallenberg virus.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of ZULVAC SBV is well described and specifications set will ensure that product of consistent quality will be produced. Conditions to the marketing authorisation were considered necessary regarding provision of data on the stability of the on-going batch production without addition of gentamicin, on the effectiveness of the antimicrobial preservative thiomersal at the end of shelf life, on batch records for a second batch of finished product and the development of a test to quantify saponin in the finished product.

For the target animal:

The product is well tolerated in the target species. The safety of ZULVAC SBV was assessed in cattle, sheep and pregnant ewes. The safety was adequately assessed in the minimum age group recommended for vaccination. Batches of ZULVAC SBV containing the maximum titre (pre-inactivation titre) and/or the maximum potency were used in sheep, cattle and pregnant ewes.

Local reactions at the injections were frequent but limited in extension and severity and overall are considered acceptable and similar to those observed for other inactivated vaccines.

The safety and efficacy of ZULVAC SBV has not been established in pregnant cattle or in lactating animals. A suitable warning has been included in the SPC.

The safety and efficacy of ZULVAC SBV has not been established in breeding males. A suitable warning has been included in the SPC.

No data on the efficacy of the vaccine in the presence of maternally derived antibodies or in seropositive animals have been presented. This has been identified as a potential risk. Given the wide distribution of the SBV across Europe, it is likely that animals to be vaccinated with ZULVAC SBV have been exposed to SBV before vaccination. A suitable warning has been included in the SPC to mitigate this risk.

For the user:

The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

For the consumer:

Residue studies are not required. The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user consumer, and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

This vaccine contains inactivated Schmallenberg virus strain BH80/11-4. It is intended to reduce viraemia associated with infection by Schmallenberg virus in cattle and to prevent viraemia associated with infection by Schmallenberg virus in sheep. The product is also effective for active immunisation of breeding sheep against SBV, to reduce viraemia and transplacental infection associated with infection by Schmallenberg virus during the first trimester of pregnancy.

The formulation and manufacture of ZULVAC SBV is well described and in general specifications set will ensure that product of consistent quality will be produced.

The product is well tolerated by the target animal.

The product presents an acceptable risk for users, consumers and the environment when used as recommended and appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature and with the condition to provide the requested data following authorisation.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP concluded that the quality, safety and efficacy of ZULVAC SBV were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for ZULVAC SBV.