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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for the granting of a community marketing authorisation for ZULVAC 1+8 Bovis (EMEA/V/C/002473)

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

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1. Summary of the dossier

ZULVAC 1+8 Bovis is a conventionally produced vaccine, liquid and ready-to-use, binary ethylenimine (BEI) inactivated, and aluminium hydroxide ($Al(OH)_3$)/saponin adjuvanted immunological veterinary medicinal product (IVMP) against bluetongue virus (BTV) serotypes 1 and 8 infections in cattle.

The application was made in accordance with Regulation (EC) No 726/2004. In view of the current concern about the spread of BTV in EU, the application is also submitted with a request for the assessment to be conducted taking into account the provisions of Article 39(7) of Regulation (EC) No 726/2004 for an authorisation under exceptional circumstances, the recommendations in the CVMP Reflection Paper on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue (EMEA/CVMP/IWP/105008/2007) and guideline EMEA/CVMP/IWP/220193/2008.

ZULVAC 1+8 Bovis contains a dose of 2 ml of iinactivated bluetongue virus, serotypes 1 and 8 and is presented in containers of 1 bottle of 10 doses (20 ml), 1 bottle of 50 doses (100 ml) and 1 bottle of 120 doses (240 ml).

ZULVAC 1+8 Bovis is recommended for the active immunisation of cattle from 3 months of age and for the prevention of viraemia induced by infection by BTV -1 and BTV -8 serotypes. The vaccine is administered by intramuscular route. The primary vaccination schedule consists of two injections of the vaccine administered to calves from 3 months of age, the second injection given 3 weeks after the initial one. The duration of immunity is 12 months.

Since there is no European Pharmacopoeia (Ph. Eur.) monograph specific to inactivated BTV vaccines, the requirements of the general monograph 0062 "Vaccines for Veterinary Use" has been taken into account for the assessment of the current authorisation. Moreover, the recommendations in CVMP Reflection Paper EMEA/CVMP/IWP/105008/2007, minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue and in the guideline EMEA/CVMP/IWP/220193/2008 on Requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue and the OIE provisions in the Manual of Standards for Diagnostic Tests have been used as reference texts for the current assessment.

A pharmacovigilance system is in place by the marketing authorisation holder and itfulfils relevant legal requirements.

2. Quality assessment

Composition

Composition for a 2 ml dose is provided in the following table:

Ingredients	Quantity per dose (2 ml)	Function	Reference to Standards
Active substance: – Inactivated bluetongue virus serotype 1, strain ALG2006/01 E1	$10^{6.7}$ to $10^{7.0}$ $TCID_{50}$ (1)	Antigen	In-house
- Inactivated bluetongue virus serotype 8, strain BEL2006/02	$10^{7.3}$ $TCID_{50}$ (1)	Antigen	In-house

Constituents of the adjuvant: – Aluminium hydroxide gel 3%	4 mg of Al^{3+}	Adjuvant	Ph. Eur. 1664
– Saponin	1 mg	Adjuvant	In-house
Constituents of the excipient: – Thiomersal	0.2 mg	Preservative	Ph. Eur. 1625
– Saline solution	*q.s.* 2 ml	Volume adjustment	In-house(2)

(1) The blending of vaccine is based on the infection titres of BTV-1 and BTV-8 antigen ($TCID_{50}$/ml) before inactivation. Calculated as indicated in Section 2.B.3
(2) Saline Solution components table

Container

The vaccine is filled in multidose high density polyethylene (HDPE) bottles (10-dose presentation (20 ml), 50-dose (100 ml) and 120-dose presentations (250 ml)). The bottles conform with Ph. Eur. 3.1.5.

The bottles are sterilised by gamma irradiation at minimum 25 kGy dose. Certificate of irradiation, HDPE bottle specifications including drawing and certificate of analysis are provided.

Development pharmaceutics

The main characteristics of the virus strains from which vaccine antigens are derived are the following:

- Serotype 1 strain BTV -1was provided by Laboratorio Central de Veterinaria (LCV, Algete, Madrid, Spain). The strain originates from an Algerian outbreak in 2006. The strain is used in the proprietary ZULVAC 1+8 Ovis vaccine.
- Serotype 8 strain BTV -8 was provided by the Belgian Veterinary Health reference laboratory VAR-CODA-CERVA (Centre d'Etudes et de Recherches Veterinaires et Agrochimiques, Ukkel, Belgium). The strain originates from a Belgian outbreak in 2006. The strain is used in the proprietary ZULVAC 8 Ovis/Bovis and ZULVAC 1+8 Ovis vaccines.

The two virus strains were propagated in BHK-21 cells for the production of the corresponding master seed virus (MSV). Working seed virus (WSV) is prepared after 3 consecutive passages from the MSV. Vaccine antigens are obtained at 5th passage from MSV on BHK-21 cells. Each virus harvest is collected, titrated and inactivated with binary ethylenimine (BEI) and then tested in accordance with the inactivation control to rule out presence of residual infectious virus particles. BEI is commonly used for immunological veterinary medicinal products and was selected due to its good efficacy and safety profile. Finally, the residual BEI is neutralised with sodium thiosulphate.

The preservative used in the formulation is thiomersal, a commonly used preservative in veterinary vaccines, of a grade that complies with the Ph. Eur. Thiomersal is included in table 1 of the annex to Regulation (EU) No 37/2010 with "no MRL required" status.

The saline solution is used as diluent of the antigen, and is added in sufficient quantity (*q.s.*) to maintain constant the quantity of antigen per dose (volume adjustment).

In order to select the adjuvant and the amount of virus in tissue culture infective dose ($TCID_{50}$), preliminary studies were carried out in sheep using experimental batches of a monovalent proprietary vaccine containing a different BTV serotype (e.g. ZULVAC 4), in order to determine the optimal qualitative and quantitative composition in terms of adjuvants and concentration of vaccine antigen. Initial immunogenicity and challenge experiments demonstrated a better performance of

BTV-4 vaccine antigen adjuvanted with a combination of aluminium hydroxide and saponin and provided some evidence for a correlation existing between antigen concentration and reduction of viraemia in 2 months old vaccinated sheep (the higher the concentration of antigen, the lower contents of viral genome). On the basis of these preliminary findings, some improvements in the manufacturing of the active ingredients were introduced and two concentrations of BTV -4 antigen were tested for safety (in 1 and 4 month(s) old sheep) and immunogenicity (in 1 month old sheep) in presence of a higher concentration of the selected adjuvants and in comparison with two oily adjuvants. Challenge experiments were carried out using the two different vaccine antigen concentrations and a selection of adjuvants (including aluminium hydroxide and saponin) showing the best safety/immunogenicity ratio. Based on the results obtained from this final study, a concentration of vaccine antigen (before inactivation) and a quantity of 4 and 0.4 mg/dose respectively of aluminium hydroxide and saponin were selected as target concentrations of vaccine antigen (before inactivation) and adjuvants in final batches of ZULVAC 4 vaccine. The information generated from these experiments was also taken into account for the development of other proprietary BTV vaccines, including the one under application, based on the fact that the same process is used for the manufacturing of the vaccine antigens, and the inactivation of BTV -1 and BTV -8 is obtained under the same conditions established for BTV -4 serotype. In addition, the same adjuvants are used. The same concentration/dose of aluminium hydroxide is used; however, the concentration of saponin per dose was increased up to 1 mg/dose. This concentration of saponin as well as the minimum concentration of each antigen (BTV-1 and BTV-8) per dose were established in the efficacy study and confirmed in another efficacy study.

The nature of the container materials (20 ml, 100 ml and 250 ml glass bottles) and of the closure system (elastomer stopper and aluminium seal) have been chosen taking into account Ph. Eur. recommendations for injectable preparations. The minimum fill volume for all presentations ensures that the stated number of doses can be recovered from the container.

Composition of the batches used in clinical trials

The vaccine batches used in the pivotal clinical trials had the same composition as indicated in this dossier with the exception of antigen content. Vaccines were produced in accordance with the method detailed in this document and are representative of commercial product. All the batches were produced in roller flasks.

It should be noted that no strategy of differentiating infected from vaccinated animals (DIVA) has been developed in conjunction with this vaccine. The nature of the inactivated vaccine means that there are currently no DIVA options associated with it.

The vaccine is blended on the basis of the pre-inactivation viral titre of the bulk antigen. This is allowed by the recommendations provided in the relevant Reflection Paper EMEA/CVMP/IWP/105008/2007 on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue and the CVMP guideline EMEA/CVMP/IWP/220193/2008 on Requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue.

Proof that the selected concentration of thiomersal is effective against the growth of representative bacterial and fungal species in accordance with the Ph Eur. monograph on efficacy of antimicrobial preservatives has been demonstrated.

Method of manufacture

The manufacturing process for BTV -1 serotype is the same as for the BTV -8 serotype in the already authorised ZULVAC -8 Bovis/Ovis and the ZULVAC 1+8 Ovis vaccines.

The manufacturing process consists of two steps: the production of the vaccine antigens, and the preparation of the finished product. Detailed flow charts of the two manufacturing steps (including reference to the controls carried out during the manufacturing process and on the finished product) were provided and considered satisfactory.

Manufacture of the vaccine antigen

The vaccine virus is grown in BHK-21 cells. A Master Seed Virus (MSV) was constituted on BHK-21 cells and stored frozen prior to vaccine production. The working seed virus (WSV) is expanded from the MSV and also stored frozen.

In the production process, the vaccine virus is produced from the WSV by a number of passages on BHK-21 cells.

The quantity of antigen per dose is calculated and adjusted in each produced batch according to the titre of the bulk antigens before inactivation. The final viral suspension is inactivated with BEI according to Ph. Eur. requirements. The excess of inactivating agent is neutralised with sodium thiosulphate at the end of the inactivation process. Samples are taken from the inactivated and neutralised antigen to carry out appropriate in process controls.

Manufacture of the inactivated and neutralised vaccine antigen

Inactivated and neutralised antigen stocks can be stored at between 2° and 8°C for a maximum of 12 months. The inactivated and neutralised antigen (active ingredient/vaccine antigen) batch size range is from 50 to 1000 litres, depending in market need based on epidemiological situation.

Antigen from different batches may be pooled after inactivation to produce final product batches.

In order to evaluate the reliability and robustness of the manufacturing process, and equivalence of antigen production in roller bottles and single use bioreactors (SUBs), a summary of critical process parameters and in-process control tests are provided., Three consecutive consistency batches of BTV -1 antigen produced in roller bottles and 3 batches in SUBs. For BTV -8 antigen, 3 batches produced in roller bottles and 1 batch in SUBs. These data confirm the consistency of the production process for the inactivated BTV -1 antigen.

Manufacture of the finished product

The manufacturing process of the final vaccine is described in sufficient details. The bulk vaccine is prepared by blending pre-determined amounts of one or a mixture of several batches of inactivated and neutralised BTV antigens with thiomersal, saline solution and adjuvants. Two alternative processes for blending can be used (single and 2-tanks manufacturing process), both of which proven to give a homogeneous and consistent final bulk. The equivalence of the two alternative blending processes was evaluated through the assessment of the documentation provided for the two monovalent ZULVAC 8 Ovis/Bovis vaccines.

. The bulk vaccine can be stored at 2-8°C for ten days until the start of the filling operation. Primary packaging elements (bottles and closures) are sterilised by validated cycles. During the packing operations the product is maintained at 20±2ºC for a maximum of 48 hours. Once filled, the finished product is stored at 2-8°C.

Validation studies

A number of studies were presented as part of the validation of the manufacturing process. The majority of the control test methods were already satisfactorily assessed during the registration process of the two monovalent ZULVAC 8 Ovis/Bovis vaccines. A major contribution to the validation of the manufacturing process and quality control is provided by the inactivation kinetics (and control of complete inactivation) and by the *in vivo* batch potency test. Both types of studies were carried out for the current vaccine, similarly to the two aforementioned monovalent vaccines.

Inactivation kinetics

The inactivation kinetic studies were conducted according to a standard method common to different BTV serotypes. This approach was satisfactorily assessed for the ZULVAC 8 Ovis/Bovis vaccines. Two inactivation kinetics studies were conducted in compliance with Ph. Eur. concerning the time required for the inactivation (not more than 67% of the duration of the inactivation process). Based on the results obtained, a maximum pre-inactivation titre was established for BTV1 and BTV8.

Control of starting materials

A detailed description of the starting materials (including information on their function, species origin and treatment before use) was provided. All starting materials were already satisfactorily addressed as the majority of comments raised for the two monovalent ZULVAC 8 Ovis/Bovis and the bivalent ZULVAC 1+8 Ovis vaccines are taken into account.

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

The documentation provided demonstrates that seed materials and other starting materials of animal origin comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01/Rev.2, Oct. 2003) and corresponding Ph. Eur. monograph.

Control tests during production

A detailed description of the in process test controls was provided. The in-process tests performed during production antigen and bulk vaccine are: Virus titration, sterility, identity, inactivation, sodium thiosulphate, absence of pestiviruses, and absence of Aujeszky's Disease virus. The general characteristics, including validation where relevant, of these methods were all satisfactory assessed or appropriately adapted in the current dossier during the authorisation process of the two monovalent ZULVAC 8 Ovis/Bovis and the divalent ZULVAC 1+8 Ovis vaccines.

Control tests on the finished product

A detailed description was provided of the control tests on the finished product (appearance, volume, identity, virus titration, identification and quantification of the adjuvant aluminium hydroxide, thiomersal, safety, sterility, absence of extraneous BTV, and pH). The general characteristics of these methods, including validation where relevant, were all satisfactorily assessed (or appropriately adapted in the current dossier) during the authorisation process of two the monovalent ZULVAC 8 Ovis/Bovis and the divalent ZULVAC 1+8 Ovis vaccines.

Description of the test for identification and quantification of saponin in the finished product and data on validation of the test was requested. The applicant has agreed to develop an alternative test for saponin quantification. A timeline for the implementation of the test could not be given, but updates will be provided annually until completed.

The results for three consecutive batches of BTV -1 antigen batches produced using both manufacturing processes (roller bottles and bioreactors) and BTV -8 antigen produced in roller bottles demonstrate the consistency of the manufacturing process. However, results for only one batch of BTV -8 antigen (250 l) produced in bioreactors are provided. The applicant has agreed to provide batch results for two batches of BTV-8 antigen produced in bioreactors at the current maximum batch size of 250 l when available post authorisation.

Data is awaited to support the consistency of production of the 1000 l bioreactor scale and the 10 doses and 120 doses presentations of the vaccine. The applicant will provide batch results for three consecutive batches of BTV -1 and BTV -8 antigen produced in 1000 l bioreactors when available post authorisation to demonstrate the validity of this bioreactor size.

Stability

Limited data were generated on the stability on the requested time points.. The applicant will provide data as soon as available. The data are expected in January 2013. The applicant also will blend two more 300 l 10 dose presentation and two more 50 dose presentation batches and to include them into the real-time stability study. After approval the applicant will place the first three manufacturing scale batches into long-term stability programme.

Furthermore, the applicant will develop a test for saponin quantification. A timeline for the implementation of the test could not be given, but updates will be provided annually until completed the stability batch of each presentation for preservative efficacy at end of shelf-life. The data will be presented when completed.

Overall conclusions on quality

Although some points for concern or clarification need to be resolved, overall, the quality part of the dossier is considered satisfactory. Based on the experience gained from the authorisation procedures of the two monovalent ZULVAC 8 Ovis/Bovis and the bivalent ZULVAC 1+8 Ovis vaccines, the remaining outstanding quality issues will be addressed through recommendations.

3. Safety assessment

The safety of ZULVAC 1+8 Bovis was evaluated according to the tests required in Directive 2001/82/EC as amended and relevant to CVMP guidelines. These tests comply with the current edition of the Ph. Eur., monograph 62, "Vaccines for Veterinary Use", specifically chapter 5.2.6, "Evaluation of Safety of Veterinary Vaccines and Immunosera." Furthermore the applicant took into account the CVMP guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue (EMEA/CVMP/IWP/220193/2008).

The safety studies were conducted using the same batch of the ZULVAC 1+8 Bovis vaccine.

The safety of administration of an overdose (although no longer required under Annex I of Directive 2001/82/EC) and repeated administration of one dose was investigated under laboratory conditions in calves of the minimum recommended age for vaccination (3 months).

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

One study was performed in order to verify the safety of the administration of repeated administration of a single dose of the vaccine ZULVAC 1+8 Bovis in 3-month-old calves. The study group was formed with Friesian calves negative for antibodies to BTV-1 and BTV-8 serotypes. Follow up after administration included blood sampling, clinical observation of animals to detect anaphylactic reactions during the hours post vaccinations, measurement of rectal temperatures on D-1, D0, D0+4h, and daily during the following four days post vaccinations. Local reactions at the injection site were recorded from D0 to D14 post vaccinations. Daily observations on the general health conditions were made during the same period. Histological examinations of the injection sites in calves were made four weeks after the third vaccination. The results did not present any general reactions (anaphylactic shock/vomiting), only transitory rectal temperature increases (mean 0.7 ºC and 0.5 ºC) after the second and third vaccination respectively on days 1 and 2 post injection, and no local reactions were observed. Post mortem histological examinations showed mild to moderate granulomatous myositis in 10-30% of the calves with an average volume less than 0.1 cm^3 (measured 4 weeks post the third administration).

Safety of one administration of an overdose

This study was performed in order to verify the safety of the administration of an overdose of the vaccine ZULVAC 1+8 Bovis in 3-month-old calves. The study group consisted in Friesian calves negative for antibodies to BTV-1.. Follow up after administration included blood sampling, clinical observation of animals to detect anaphylactic reactions during the hours after vaccination, measurement of rectal temperatures on D-1, D0, D0+4h, and daily during the following four days. Local reactions at the injection site were recorded from D0 to D14 after vaccination or until total disappearance of the reactions. Daily observations on the general health conditions were made during the same period. Results showed that the calves did not present any general reactions (anaphylactic shock/vomiting). The overdose of the vaccine ZULVAC 1+8 Bovis induced a slight and transient significant mean rectal increase of 1.3 ºC in the vaccinated calves 24 hours after inoculation (all vaccinates reacted). On day 2 after vaccination rectal temperatures had normalised.

Based on the above described results, the safety profile of ZULVAC 1+8 Bovis with respect to repeated single dose administration and overdose administration in the target species from the minimum age is considered to be correctly reflected in the SPC.

Examination of reproductive performance

No study on the examination of reproductive performance in dairy cattle under field conditions after administration of a double dose was provided, however the preliminary results of such a study were submitted earlier by the company during the authorisation procedure for the vaccine ZULVAC 1 Bovis

The applicant informed the CVMP that a study investigating the safety and reproductive performance of the vaccine Zulvac 1+8 Bovis in dairy cows including pregnant and lactating cows under field conditions is planned to run from December 2011 until November 2012.

The CVMP agreed that the marketing authorisation holder is required to demonstrate safety in the field including pregnant and lactating cows, using the correct formulation of the vaccine in the present application. This requirement was entered under Annex II of the CVMP Opinion as a specific obligation of the authorisation under exceptional circumstances. The results from this safety study will be assessed at the first annual re-assessment.

Overall conclusions on safety

The safety of administration of an overdose (although no longer required under Annex I of Directive 2001/82/EC) and repeated administration of one dose was investigated under laboratory conditions in calves of the minimum recommended age for vaccination (3 months). Based on the results of these studies, the safety profile of ZULVAC 1+8 Bovis with respect to repeated single dose administration and overdose administration in the target species from the minimum age is considered to be correctly reflected in the SPC.

No study on the examination of reproductive performance in dairy cattle under field conditions after administration of a double dose was provided, however this was addressed through the addition of a specific obligation to provide the results of such a study for the first annual re-assessment.

The safety of ZULVAC 1+8 Bovis was therefore not established in breeding animals and this is reflected in the SPC. No information is available on the use of ZULVAC 1+8 Bovis with any other product. Therefore, a decision to use this vaccine before or after any other veterinary medicinal product needs to be made on a case by case basis. User safety

A detailed user risk assessment taking into account direct contact with the product and its components has been provided. The CVMP concluded that the nature and concentration level of the constituents, are not susceptible to cause a hazard to the user. The actual risk is reflected using the word "Negligible" in the SPC.

Consumer safety

No withdrawal period is required for this vaccine. In conclusion, the safety profile of ZULVAC 1+8 Bovis is considered to have been adequately reflected under the relevant sections of the SPC.

It has been demonstrated that there are no residues left from vaccination in meat which would present a risk to the consumer.

Zulvac 1+8 Bovis is an inactivated vaccine, therefore there is no risk of any residual live organism or vaccines residues in the meat of food producing species with this kind of vaccine.

Environmental Risk Assessment

An assessment of the potential risk to the environment has been conducted, in accordance with the Note for Guidance: Environmental Risk Assessment for Immunological Veterinary Medicinal Products (EMEA/CVMP/074/95). The risk was regarded as negligible and therefore a Phase II assessment deemed not necessary.

4. Efficacy assessment

Introduction and general requirements

ZULVAC 1+8 Bovis is recommended for the active immunisation of cattle from 3 months of age for the prevention of viraemia caused by bluetongue virus, serotypes 1 and 8. A 2 ml dose of the vaccine is recommended to be administered by the intramuscular route to cattle. In the SPC it is stated that safety in pregnant animals has not been studied and it should be used only after benefit/risk assessment of the responsible veterinarian. The basic vaccination schedule consists of one initial injection from 3 months of age followed by a second injection administered 3 weeks later. Onset of immunity is 21 days after completion of the primary vaccination course. The absence of any investigation of the influence of maternally derived antibodies (MDA) on the efficacy of the vaccine is reflected in a statement included in the SPC. Field trials were not strictly required for this type of application. A DIVA strategy has not yet been implemented.

The challenge strains used in the efficacy studies were homologous to the vaccine strains which has been considered justified by the applicant due to the emergency nature of the studies and the lack of time to source and validate a suitable heterologous strains. This approach was already accepted for other ZULVAC Bluetongue vaccines (in sheep and cattle) as being representative of the present European situation to BTV-1 and BTV-8 serotypes.

The applicant has developed a challenge model, in order to inoculate an amount of virus so that all control animals become viraemic during the study, since the target aim of ZULVAC 1+8 Bovis was "prevention of viraemia in vaccinated animals".. For 27 days after challenge, animals were monitored for the appearance of major clinical signs. Blood samples for assessing presence of viraemia were periodically collected after challenge. The model was able to show that all the unvaccinated and challenged animals from several studies carried out with vaccines against BTV -1 and BTV -8 became viraemic . This model was then used for challenge of the target animals in order to define onset and duration of immunity for ZULVAC 1+8 Bovis.

Laboratory Trials

Study of the efficacy of different antigen concentrations and different adjuvant compositions of ZULVAC 1+8 Bovis

This study aimed to evaluate the efficacy of different antigen concentrations and different adjuvant compositions of ZULVAC 1+8 Bovis vaccines in order to establish the lowest vaccine concentration able to prevent viraemia (presence of genome in blood) in vaccinated calves. Five vaccines were tested . Of these, only one batch represented the final formulation of the vaccine, while the other vaccines included lower levels of the adjuvant Saponin or a different adjuvant. Likewise the antigen concentrations of BTV-8 varied in the tested vaccine combinations while the antigen concentration of BTV-1 was stable in all five vaccines.

A mixed group of calves, 2.5 - 4 months of age and tested negative for antibodies to BTV-1 by ELISA were included in the study. Six groups of calves were made and each of the groups 1-5 was vaccinated and revaccinated according to the proposed vaccination scheme with one of the 5 vaccines Calves in group 6 served as non vaccinated controls.

Two challenges were conducted. Twenty five days after revaccination calves from groups 1, 2, 3 and 4 and 6 were challenged with either BTV -1 or BTV -8 (half of the calves with each serotype). The second challenge was conducted on day 58 after revaccination, when calves from group 5 and 6 were challenged with either BTV -1 or BTV -8 (half of the calves were challenged with each serotype).

The challenge load was 2 ml of BTV-1 challenge virus - for BTV-8 respectively via intravenous route. The calves were monitored after each injection for the appearance of any systemic reactions associated with the administration of vaccine in calves (anaphylactic shock, anorexia, etc.). Rectal temperature was measured before each injection, at D0+4h and daily during the next two days. Injection site reactions were observed post vaccination for 14 days after each injection, blood samples were taken on D0 (before 1st vaccination), D28, D35 and D42 in order to evaluate the serological response (neutralising antibodies) after vaccination. After challenge, blood samples were taken from the animals on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post infection for the evaluation of presence of the BTV genome by real time RT-PCR. The animals were monitored on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post challenge for the appearance of clinical signs associated with the disease (rectal temperature, nasal and/or ocular discharge, nasal and/or ocular oedema, lameness and prostration).

Results showed that viraemia was prevented in two of the vaccines tested namely ZULVAC 1+8 Bovis, where the vaccines induced the highest immune response, being able to prevent viraemia in 100% of the calves. Viral genome had not been detected by real time RT-PCR technique during the 28 days post challenge in these two vaccines while the other three combinations showed to be less protective. Both challenge serotypes induced very mild clinical signs in non-vaccinated control calves. No anaphylactic reactions were provoked from any of the five vaccine combinations. Rectal temperatures were only slightly increased in the controls after challenge compared to vaccinates and calves did not manifest local reactions at the injection site. Onset of immunity was therefore supported to start from 26 days after completion of the initial vaccination scheme.

Another study also aimed to evaluate the efficacy of different antigen concentrations and different adjuvant compositions of ZULVAC 1+8 Bovis vaccines in order to establish the lowest vaccine concentration able to prevent viraemia (presence of genome in blood) in vaccinated calves. Four vaccines were tested. Of these only one represented the final formulation of the vaccine, while the other vaccines included a different adjuvant or a lower level of BTV-8 antigen.

A mixed group of calves, 2.5 – 3.5 months of age and tested negative for antibodies to BTV by ELISA were included in the study. The calves were divided in 5 groups and each of the groups 1-4 was vaccinated and revaccinated according to the proposed vaccination scheme with one of the 4 batches. Calves in group 5 served as non vaccinated controls. The calves were randomly selected for challenge studies.

The challenge study was conducted one time with both serotypes of BTV. Twenty one days after revaccination calves from groups 1 and 3 and calves from groups 2, 4 and 5 respectively were challenged with either BTV -1 or BTV -8 (half of the calves with each serotype). Calves that were not challenged were taken out of the study.

The challenge load was 2 ml of BTV -1 and BTV -8 challenge viruses - via intravenous route per animal. The calves were monitored after each injection for the appearance of any systemic reactions associated with the administration of vaccine in calves (anaphylactic shock, anorexia, etc.). The rectal temperature was measured before each injection, at D0+4h and daily during the next two days. Injection site reactions were observed post vaccination for 14 days after each injection, blood samples were taken on D0 (before 1st vaccination), D28, D35 and D42 in order to evaluate the serological response (neutralising antibodies) after vaccination. After challenge, blood samples were taken from the animals on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post infection for the evaluation of presence of the BTV genome by real time RT-PCR. The animals were monitored on days days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post challenge for the appearance of clinical signs associated with the disease (rectal temperature, nasal and/or ocular discharge, nasal and/or ocular oedema, lameness and prostration).

Results showed that viraemia was prevented in3 of the 4 vaccines tested namely ZULVAC 1+8 Bovis. Viral genome had not been detected by real time RT-PCR technique during the 28 days post challenge in these two vaccines while the other three combinations showed to be less protective. Calves vaccinated with the vaccine presented the highest serological response after vaccination. The challenge serotypes did not induce clinical signs in non-vaccinated control calves and no anaphylactic reactions were provoked from any of the five vaccine combinations. Rectal temperatures were only slightly increased in the controls after challenge compared to vaccinates and calves did not manifest local reactions at the injection site. Onset of immunity was therefore supported to start from 21 days after completion of the initial vaccination scheme.

Influence of maternal antibody on the efficacy of the vaccine

Studies have not been conducted in animals with maternal antibodies. Therefore the following warning has been included in section 4.4 of the SPC: "No information is available on the use of the vaccine in seropositive animals including those with maternally derived antibodies".

Duration of immunity

A new study was submitted to support duration of immunity of 12 months therefore the wording of the SPC, now reflects this period.

Field Trials

No field trials were performed. According to the CVMP guideline on minimum data requirements for an authorization under exceptional circumstances for vaccines for emergency use against BT disease,, specific field trials are not a required.

Overall conclusion on efficacy

The onset of immunity is 21 days after completion of the primary vaccination course, and duration of immunity is 12 months. Laboratory efficacy trials support the claim, onset and duration of immunity of the ZULVAC 1+8 Bovis vaccine.

In the absence of any specific data, and consistent with the approach followed for other ZULVAC B TV serotype monovalent and bivalent vaccines, the following statement was agreed to be used in the SPC: "Any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian, taking into account the local epidemiological situation".

Within the context of an authorisation given under exceptional circumstances, and consistent with the provisions in the relevant guideline and the inclusion of specific warnings in the relevant sections of the SPC, the efficacy of the product can be considered as acceptable.

5. Benefit risk assessment

Direct benefits

The benefit of the product is prophylactic immunisation to protect cattle against infection with BTV serotypes 1 and 8. The vaccine has been proven to prevent viraemia. Prevention of viraemia directly benefits the animal in that this ensures reduction of clinical signs or loss of condition.

Onset of immunity is 21 days after the completion of the basic vaccination scheme. The duration of immunity is 12 months.

Indirect or additional benefits.

In addition to the direct benefit to the vaccinated animal, there is a benefit to herd health both locally and regionally. As BTV is an arthropod borne disease an animal needs to be viraemic for the insect vector to pick up the BTV virus, therefore as ZULVAC 1+8 Bovis prevents viraemia it is also able to prevent disease transmission and spread.

The use of vaccines such as ZULVAC 1+8 Bovis is important at a community animal health level as they are the most effective way to control disease spread as there are no efficient ways to control the insect vector and no therapeutic treatment for BTV infections. Vaccination has been shown to be an efficient tool for disease control.

Effective vaccination of cattle against bluetongue could benefit individual farmer and national economy and be a valuable tool for safe trade of live animals according to OIE rules or EU legislation.

Risk assessment

The risk to the target animal can come from three sources:

Firstly, from extraneous agents or contaminants in starting materials or from incomplete inactivation of the live virus. This risk is mitigated by the control of the production process and starting materials to ensure no contaminants are present, by validation of in-process and final product tests and by using a validated inactivation process

Secondly, as an adverse reaction in the target animal in response to vaccination. There are limited local reactions after vaccination, and these are appropriately indicated on the SPC as set out in the introduction. These local reactions have no effect on the general systemic health of the animals and are in line or less than those observed with other vaccines for cows. Safety studies demonstrates that the product is safe in minimum age animals.

Thirdly, the risk of lack of efficacy. No significant risk was identified according to the studies presented. This onset of immunity has been fully documented using challenge studies. The duration of immunity of 1 year has been fully established.

A full user risk assessment is provided in the assessment report which concludes that the active ingredient and excipients do not present a risk to the user.

The environmental risk assessment provided, demonstrates that ZULVAC 1+8 Bovis contains no ingredients which are considered harmful to the environment.

With respect to residues from vaccination, this is addressed in detail in the assessment report and it has been demonstrated that there are no residues left in meat which would present a risk to the consumer.

Additional risk associated with vaccines are reversion to virulence and spread of vaccine strain, ZULVAC 1+8 Bovis is an inactivated vaccine therefore there is no risk associated with this product.

Conclusion on benefit risk balance

While the information provided in the dossier (quality, safety and efficacy) is not sufficient for an standard marketing authorisation it does confirm an overall positive benefit risk balance under exceptional circumstances given the epidemiological situation of bluetongue serotypes 1 and 8. The marketing authorisation holder will address the specific obligations and any deficiencies in the data submitted within a predetermined post authorisation timeframe. No significant risks were identified when the product is used as indicated in SPC and under normal veterinary practice conditions.

ZULVAC 1+8 Bovis is well tolerated by the target animals and presents a low risk for the users and the environment. It has shown to be efficacious for the active immunisation of cattle from 3 months of age for the prevention of viraemia caused by BTV -1 and BTV -8 serotypes. Onset and duration of immunity is at 21 days and 12 months, respectively, after the completion of the basic vaccination.

Conclusion

The CVMP considered that due to the current epidemiological situation of bluetongue regarding serotypes 1 and 8 and the consequent threat to animal health there are objective and verifiable reasons for recommending the granting of a marketing authorisation under exceptional circumstances for this product, namely:

- Bluetongue disease is spread by insect vectors and therefore presents particular challenges in terms of control due to an inability to prevent transmission from infected animals other than through insect control combined with reducing or preventing viraemia (virus in the blood) in susceptible animals by means of vaccination;
- Bluetongue disease is epizootic in nature and has the potential to result in high morbidity and mortality in susceptible populations;
- There is still a small number of vaccines against bluetongue in Europe authorised via the centralised procedure.
- That the application has met the requirements of the CVMP guideline on Minimum Data Requirements for an Authorisation under Exceptional Circumstances for Vaccines for Emergency use against Bluetongue (EMEA/CVMP/IWP/220193/2008);
- That consequently any delay should be avoided where possible in making available safe and effective vaccines that have been demonstrated to be in compliance with the CVMP guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue (EMEA/CVMP/IWP/220193/2008).
- That the marketing authorisation holder has agreed to the necessary specific obligations, to assure the safe use of the product in the field.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the ZULVAC 1+8 Bovis is approvable and were considered to be in accordance with the requirements of Article 39(7) of Regulation (EC) No 726/2004 for an authorisation under exceptional circumstances. The recommendation can be made for a marketing authorisation under exceptional circumstances.