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Veterinary Medicines and Product Data Management

Scientific discussion

1. Summary of the dossier

ZULVAC 1 Bovis is a conventionally produced, liquid and ready-to-use, inactivated vaccine, adjuvanted with aluminium hydroxide/saponin. The active substance of ZULVAC 1 Bovis is inactivated Bluetongue virus (BTV), serotype 1, an immunological veterinary medicinal product (ATCvet Code QI02AA08) which acts by the development of active immunisation of cattle and preventing viraemia induced by BTV serotype 1 infection. The product is presented as a suspension for injection.

The vaccine was eligible for the granting of a Community marketing authorisation via the centralised system in accordance with Article 3(2) of Regulation (EC) No 726/2204 (immunological veterinary medicinal products for the treatment of animal diseases subject to Community prophylactic measures).

The application was made in line with the requirements of the CVMP guideline on Minimum Data Requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue disease (EMEA/CVMP/IWP/220193/2008).

The benefits of ZULVAC 1 Bovis are its prophylactic immunisation to protect cattle from 2.5 months of age against infection with BTV serotype 1. 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.

The most common side effect is a transient increase in rectal temperature after injection and then return to normal values. No adverse reactions (general or local reaction) were observed after the 1st, 2nd and 3rd administration of a single dose of vaccine to calves.

Epidemiology of BTV in the EU has considerably changed in the last ten years as a consequence of the incursion of different BTV serotypes in regions of the Community, where outbreaks have never been reported before and which were not considered at risk. Climate changes affecting the hydrology and ecosystems in many regions of the world, including Europe, and the finding that new species of Culicoides (such as indigenous European insects) are likely to be involved in the transmission, are suspected to have driven the spread of different BTV serotypes in Europe.

The serotype 1 (BTV-1) was first reported in Greece, in a brief epidemic in 2001. It has been demonstrated by molecular studies that the virus strain was of Eastern origin. The current epidemic in the West Mediterranean Region started after five years. According to OIE, BTV-1 was first reported in Algeria (June 2006) and a few months later in Morocco, Tunisia and Italy (Sardinia) and later it spread

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to Spain, Portugal and France. The virus strains were found close to the prototype South African BTV-1 strain (Western).

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 (BTV), serotype 1, strain ALG2006/01 E1	RP ≥ 1[(1)]	Antigen	In-house
Constituents of the adjuvant: Aluminium hydroxide hydrated for adsorption	4 mg Al^{3+}	Adjuvant	Ph. Eur. 1664
Saponin	0.4 mg	Adjuvant	In-house
Constituents of the excipient: Thiomersal	0.2 mg	Preservative	Ph. Eur. 1625
Saline solution	*q.s.* 2 ml	Diluent	In-house

[(1)]Relative potency by a mice potency test compared to a reference vaccine that was shown efficacious in cattle.

Container

The vaccine is filled in multidose type I hydrolytic glass bottles (10-dose presentation (20 ml)) or type II hydrolytic glass bottles (50-dose presentation (100 ml) and 120-dose presentation (240 ml)). The bottles conform with European Pharmacopoeia (Ph. Eur.) monograph 3.2.1. They are closed with a chlorobutyl rubber stopper, (Ph. Eur. monograph 3.2.9) and sealed with an aluminium cap. The product is packaged together with a product information leaflet.

Development Pharmaceutics

ZULVAC 1 Bovis is an inactivated and adjuvanted vaccine for the prevention of the viraemia against Bluetongue virus serotype 1 (BTV-1). The strain originates from an Algerian outbreak in 2006 and is the same vaccine strain used for the proprietary's ZULVAC 1+8 vaccine which has already obtained an authorisation under exceptional circumstances.

Sequence analyses of genome segment 2 of the Algerian BTV-1 virus shows it to be very closely related to the subsequent 'Western' isolates of BTV-1 from Europe (2007 onwards) but it is distinct from the "Eastern" strains of BTV-1 previously isolated in Greece (in 2001). However, because of the prevalence of other BTV strains in north Africa and Europe (e.g. BTV-4, and BTV-8), it is possible that the later isolates of BTV-1 from Spain, Portugal and France may have exchanged some genome segments by reassortment. Only a full genome analysis of each isolate could reveal this (this has not been done). Since the identity of the European isolates that were identified as BTV-1 (after 2006) is based on Seg-2, which also determines the specificity of neutralisation and virus serotype, it is clear that the vaccine strain of BTV-1 from Algeria should cross-protect fully against all of the later European BTV-1 isolates, even if they are reassortants.

The virus strain was propagated in BHK-21 cells for the production of the master seed virus (MSV). The working seed virus (WSV) is prepared from the MSV. Vaccine antigens are obtained after some passages from MSV on BHK-21 cells. The virus harvest is titrated, and before the formulation of the vaccine, the virus harvest is inactivated with binary ethylenimine (BEI) then tested in accordance with the inactivation control, to rule out presence of residual infectious virus particles.

The adjuvant system used in the formulation of the vaccine was selected according to the results obtained within the frame of the development of ZULVAC 4, an inactivated vaccine against BTV-4 which was granted an authorisation by Spanish authorities in August 2007. The preservative used in the formulation is thiomersal, a commonly used preservative in veterinary vaccines, of a grade that complies with the relevant monograph of the Ph. Eur. The saline solution is used as diluent of the antigen, is added in sufficient quantity (q.s.) to maintain a constant number of viral particles per dose.

Preliminary studies were carried out in sheep using experimental batches of a monovalent proprietary vaccine containing a different BTV serotype, 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 was the viraemia). 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 the safety and immunogenicity in the 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 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. 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 antigen, and the inactivation of BTV-1 is obtained under the same conditions established for BTV-4 serotype. In addition, the same adjuvant(s) at the same concentration(s)/dose are used.

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.

Composition of the batches used in clinical trials

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.

Satisfactory 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 was provided.

Method of manufacture

The description of the manufacturing process of the antigen was very detailed and precise. It took into account the majority of the comments raised for the two monovalent ZULVAC 8 Ovis/Bovis and the bivalent BTV 1+8 vaccines.

The manufacturing process consists of two steps: the production of the vaccine antigen, and the preparation of the finished product. The process starts with the propagation of the WSV and ends with the preparation of the vaccine in bulk, followed by filling and packing of the final product. The production system and control guarantees the traceability of each component during the manufacturing process. After harvest, the culture is inactivated and the inactivant neutralised at the end of the inactivation process. The bulk vaccine is further produced after blending a pre-determined amount of inactivated and neutralised vaccine antigen, thiomersal, saline solution and adjuvants.

Manufacture of the vaccine antigen

Vaccine virus is grown in BHK-21 cells. The MSV was constituted on BHK-21 cells and stored frozen prior to vaccine production. The WSV is expanded from the MSV and also stored frozen.

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

Manufacture of the inactivated and neutralised vaccine antigen

The final viral suspension is inactivated with BEI according to Ph. Eur. requirements. The excess of inactivating agent is neutralised at the end of the inactivation process. Samples are taken from the inactivated and neutralised antigen to carry out appropriate in process controls.

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 on market need based on the 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 from 3 consecutive batches of the antigen produced in roller bottles and 3 produced in SUBs were provided. These data confirm the consistency of the production process for the inactivated BTV-1 antigen.

Manufacture of the finished product

The description of the manufacturing process of the finished product has been described in detail and overall, is very precise. 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 are 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 ZULVAC 8 Ovis/Bovis vaccines already authorised for use in sheep and cattle.

The bulk vaccine can be stored at 2 - 8 °C for 10 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 ± 2 ºC 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 authorisation 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, as for 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 and it has proven to be sufficiently sensitive, as it was 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). Inactivation kinetics were tested using a BTV-1 suspension with a titre representative of routine production batches (i.e. reference batch), followed by inactivation kinetics of 10x concentrated BTV-1 suspension. Based on the results of the second study a maximum pre-inactivation titre was established for BTV-1 serotype.

Control of starting materials

Active substance and Excipients

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

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

The documentation provided demonstrate 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.

The starting materials of animal origin used in the production of the final product comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01 Rev.2) and Commission Directive 1999/104/EEC.

Control tests during production

A detailed description of the in-process tests 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 as a result of the authorisation process of the two monovalent ZULVAC 8 Ovis/Bovis vaccines. The results of the control testing carried out on three consecutive batches of BTV-1 antigen, produced using both roller flasks and bioreactors manufacturing processes, have been provided and were found compliant with the established specifications.

Control tests on the finished product

A detailed description was provided of the control tests on the finished product (appearance, volume, identity, *in vivo* potency, identification and quantification of the adjuvant aluminium hydroxide, identification and quantification of the adjuvant saponin, thiomersal, safety, sterility, absence of extraneous BTV, and pH). The general characteristics of these methods, including validation where relevant, were all satisfactorily assessed during the authorisation process of the two monovalent ZULVAC 8 Ovis/Bovis vaccines. The specifications proposed at release and end-of-shelf life are appropriate to control the quality of the product.

The consistency of the manufacturing process has been demonstrated for three consecutive batches of BTV-1 antigen (produced in roller bottles) and 3 consecutive batches of the 50 dose presentation of the vaccine.

Data are awaited to support the consistency of production of the 1000 litres bioreactor scale and the 10 dose and 120 dose presentations of the vaccine. The results for the pilot scale batches of the 10 dose and 120 dose presentations included in the stability study demonstrate consistency of the manufacturing process. Consistency will be confirmed by submission of batch results from the first three manufacturing scale batches of each presentation manufactured according to the 250 litres scale and data on 3 antigen batches between 250 - 1000 litres post authorisation.

Once authorised, the applicant is recommended to provide the results of the batch potency test in transgenic mice carried out on (at least) the first 10 batches of ZULVAC 1 Bovis vaccine. Data will be provided at each annual assessment until data on a sufficient number of batches have been provided. Taking the substantial variability observed for the reference vaccine, the scope of the *in vivo* test and the 3R principle into consideration, the applicant was requested to establish an alternative *in vitro* batch potency test; updates on the development of the alternative potency test will be provided at each annual assessment.

The CVMP agreed to the provision of a validated test to quantify the saponin content in the finished product after authorisation.

Stability

Limited data were generated on the stability of the antigen and finished product at any of the requested time points. This is provisionally acceptable, and according to the relevant guideline interim 12 months stability for the finished product may be assigned. The full set of stability data will be submitted when available post authorisation. Data demonstrating the efficacy of the antimicrobial preservation during the whole shelf life of the vaccine are provided.

Overall conclusion on quality

Overall, the quality part of the dossier can be considered sufficiently clear and complete. Quantitative and qualitative particulars of the constituents are indicated. The manufacturing method is sufficiently described and relevant in-process controls are performed. Starting materials are sufficiently controlled. Seed materials and other starting material of animal origin relevant for the transmission of TSE comply with the guideline (EMEA/410/01-Rev2) and the corresponding Ph. Eur. monograph. With regard to the final product testing and stability testing, the applicant has agreed to a list of recommendations that will be provided post authorisation. All this assurance was considered sufficient for granting a marketing authorisation under exceptional circumstances, but not for a full marketing authorisation.

3. Safety assessment

In order to comply with the current legislation, the safety of the administration of one dose, of repeated administration of one dose and of an overdose of the vaccine under application was assessed under laboratory conditions, in calves of the minimum age recommended for vaccination. The safe use of the vaccine in pregnant cows was examined in a study farm under restricted conditions. In this category of the target animal species, the safety of the administration of an overdose of the vaccine was also investigated. The aforementioned tests were carried out following the 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.

Laboratory tests

Safety of one administration of an overdose

One study was performed in order to verify the safety of the administration of an overdose of the vaccine ZULVAC 1 Bovis in 2.5 months-old calves. 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 4 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), no temperature increase, and no local reactions. Another 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 cows. Follow up administration included bloody 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 4 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 general health 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 transitory significant mean rectal increase of 0.7 ºC in the vaccinated calves 24 hours after inoculation. On day 2 after vaccination rectal temperatures had normalised.

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

This study was performed in order to verify the safety of repeated administration of a single dose of the vaccine ZULVAC 1 Bovis in 2.5-3 months old calves. A group of Friesian calves negative for antibodies to BTV-1 were included, of these 70% were administered a single dose three times with three week intervals. The other 30% of the calves were administered phosphate buffered saline (PBS) solution at single dose level at the same time points. 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 after each vaccination. Local reactions at the injection site were recorded from D0 to D14 after vaccination or until total disappearance of the reactions. Daily observations on general health were made during the same period. Five weeks after the 3rd administration of vaccine all calves were euthanized and macroscopic examination of the injection site was performed. Results showed that 3 times repeated administration of a single dose of ZULVAC 1 Bovis at its maximum potency did not induce any anaphylactic reactions, no statistically significant differences in rectal temperatures

between vaccinates and controls at any time points after vaccination, and no local reactions at the injection site. Post mortem inspections revealed no macroscopic tissue lesions at the injection site.

Another study was performed in order to verify the safety of repeated administration of a single dose of the vaccine ZULVAC 1+8 Bovis in 3 months old calves. Two groups of Friesian calves negative for antibodies to BTV-1 were included. Calves in group 1 were administered a single dose three times with three week intervals. Calves in group 2 were administered PBS at single dose level at the same time points. 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 after each vaccination. Local reactions at the injection site were recorded from D0 to D14 after vaccination or until total disappearance of the reactions. Daily observations on general health were made during the same period. Five weeks after the 3rd administration of vaccine all calves were euthanized and macroscopic examination of the injection site was performed. Results showed that three times repeated administration of a single dose of ZULVAC 1+8 Bovis at its maximum potency did not induce any anaphylactic reactions. The vaccine did not induce hyperthermia in the calves, except for a transitory rectal temperature increase of 0.4 ºC recorded in the vaccinated calves 24 hours after the 2nd vaccination. Two days after vaccination, rectal temperatures had normalised. No local reactions were recorded at the injection site. Post mortem inspections revealed no macroscopic tissue lesions at the injection site.

Based on the above described results, the safety profile of ZULVAC 1 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

An interim report of an ongoing study on reproductive performance after administration of a double dose in dairy cattle under field conditions was provided. The study started in June 2010 and is still pending with expected finalisation in the first quarter of 2011. Two parallel groups were formed by means of a double blinding system. Group A cows were vaccinated with a double dose of ZULVAC 1+8 and group B received placebo. Standard safety observations of increases in rectal temperatures were made on D-1, D0, D0+4h and D1-D4. Local reactions at the injection site were also recorded as standard in a percentage of cows including heifers and young cows.

During the study, records were kept of other safety parameters in the vaccinated cows (i.e. milk production and reproduction parameters, number of preterm and full-term calves, physiological condition of calves at birth, percentage of pregnant cows post insemination, number of births and abortions) which will be compared with the data obtained from the cows inoculated with PBS only (control animals).

Results until now have shown that the overdose did not induce general reactions such as anaphylaxis or vomiting. Statistically significant higher rectal temperature was observed in vaccinated cows at D+1 PV (p-value= 0.001) with a rectal temperature increase of up to 2.1° C. For the rest of the time points, no differences between vaccinated and controls were observed. Vaccination resulted in a local reaction at the injection site in 37.5% of vaccinates. Local reactions were also observed in the control group in 26.9% of the animals. The reactions in the vaccinated animals were in most cases observed as palpable nodules < 2 cm in diameter (in 1 animal > 2 cm in diameter). A nodule of ≤ 0.5 cm persisted for more than 36 days in 1 cow (4.2%). The SPC, section 4.10 has been updated with respect to increases in rectal temperature after vaccination as these results are final at the present time. The applicant is recommended to revise the SPC, section 4.10 when the field study has ended with respect to the frequency of local reactions.

Final results with respect to production results from the study are awaited and should be provided as soon as possible after finalising the study. The applicant has agreed to provide the final study report on production results.

The safety of ZULVAC 1 Bovis was not investigated in breeding males, which is reflected correctly in the SPC, section 4.7. In conclusion, the safety profile of ZULVAC 1 Bovis is considered to have been adequately reflected under the relevant sections of the SPC.

Studies on immunological functions have not been conducted which is acceptable as the vaccine is inactivated and the adjuvant has been shown to be safe.

No data are available on the use of ZULVAC 1 Bovis with any other product therefore an appropriate warning has been included under section 4.8 of the SPC.

User safety

A detailed risk assessment concerning the risk put to any human beings in direct contact with the product and derived from its components has been made. It was concluded that the nature and concentration level of the constituents, are not susceptible to cause any hazard to the user. The actual risk of human exposure is limited to the person injecting the product to the animals (veterinarians, or experienced persons working under the direct supervision of a veterinarian), however the amount and method of administration does not pose any additional risks compared to other injectable products to animals and humans. In the absence of any demonstrated risks, according to the provisions in the User Safety Guideline for Immunological Veterinary Medicine Products (IVMPs), (EMEA/CVMP/54533/06), the recommended conditions of use are adequately reflected in the relevant section of the SPC.

Withdrawal period

The withdrawal period for ZULVAC 1 Bovis for meat and milk is zero days.

Environmental safety

An assessment of the potential harmful effects to the environment was conducted in accordance with requirements of the Note for Guidance: Environmental Risk Assessment (ERA) for Immunological Veterinary Medicinal Products (EMEA/CVMP/074/95). This risk was regarded as negligible on the grounds of the nature (inactivated vaccine), and composition of the vaccine under study. Therefore a Phase II assessment was not necessary. The excipients consist of substances that will likewise not be excreted into the environment. Although ZULVAC 1 Bovis is contained in glass bottles, vial breakage or spilling of vaccine, will not lead to major consequences, as the amounts will be very small, hence the general risk posed to the environment by the use of the vaccine under study is negligible.

In sum, due to the robust manufacturing process, including a fully validated inactivation test and control of inactivation, the risk arising from the presence of live Bluetongue virus in the vaccine and its excretion into the environment is negligible.

Overall conclusions on safety

The safety of ZULVAC 1 Bovis was assessed taking account of the guidance on combined vaccines (CVMP/IWP/52/97) and using a bivalent vaccine containing BTV-1 and BTV-8 in order to demonstrate safety of the monovalent BTV-1. Both vaccines contain the same amount of BTV-1 antigen, adjuvant and excipients; therefore, data were directly relevant.

The safety of administration of an overdose (although no longer required under Annex I to Directive 2001/82/EC as amended) and repeated administration of one dose was investigated under laboratory conditions in calves of the minimum recommended age for vaccination. The safe use in dairy cows under field conditions was investigated by administration of an overdose of ZULVAC 1+8 Bovis, but the study is still pending, therefore, production results have not yet been obtained. This study is expected to be finalised during first quarter of 2011. The applicant is recommended to submit results from the double dose field study in dairy cattle when the study has ended. According to the CVMP guideline on Minimum Data Requirements for an authorisation under exceptional circumstances for vaccines for emergency use against BT disease, field studies were not performed. The potential for any adverse effects following the administration of the vaccine under the recommended conditions of use is adequately reflected in the relevant section of the SPC.

Overall, the safety profile of ZULVAC 1 Bovis vaccine was demonstrated. In the absence of any demonstrated risks, according to the provisions in the User Safety Guideline for Immunological Veterinary Medicine Products (IVMPs), (EMEA/CVMP/54533/06), the recommended conditions of use are equally reflected in the relevant section of the SPC.

4. Efficacy assessment

Introduction and general requirements

ZULVAC 1 Bovis is recommended for the active immunisation of cattle from 2.5 months of age for the prevention of viraemia caused by BTV, serotype 1. A 2 ml dose of the vaccine is recommended to be administered by the intramuscular route to cattle (including pregnant animals). The basic vaccination schedule consists of one initial injection from 2.5 months of age followed by a second injection administered 3 weeks later. Onset of immunity is 15 days after completion of the primary vaccination course and duration of immunity is 12 months. Annual revaccination is recommended. 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 differentiation of infected from vaccinated animals (DIVA) strategy has not yet been implemented.

The challenge strain used in the efficacy studies is homologous to the vaccine strain 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 strain. This is considered justified to ensure that the vaccine strain is representative for the European situation for BTV-1.

Laboratory studies

The applicant 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 of BTV vaccines was "prevention of viraemia in vaccinated animals". 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 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 Bovis.

Study of the efficacy of two different antigen concentrations in ZULVAC 1 Bovis

This study aimed to evaluate the efficacy of two different antigen concentrations in ZULVAC 1 Bovis vaccine in order to establish the lowest vaccine concentration, able to prevent viraemia in vaccinated calves. Three groups of calves were made. Calves in groups 1 and 2 were vaccinated and revaccinated

after three weeks with two different BTV-1 vaccines. 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 and D35 (the day prior to challenge) and measured serological responses by ELISA and serum neutralisation (SN). After challenge, blood samples were extracted from the animals on days 3, 5, 7, 8, 11, 14, 18, 21, 25 and 28 post challenge, for the evaluation of presence of the BTV genome by real time RT-PCR. The animals were monitored daily during 15 days post challenge for the appearance of clinical signs associated with the disease (rectal temperature, nasal and/or ocular discharge, coughing, dyspnoea, limping, and prostration). Results showed that viraemia was prevented in both tested vaccines. The two tested vaccines induced a significant post-vaccination serological response (antibody titre detected by ELISA and SN) in the animals. Rectal temperatures were not statistically raised in vaccinates and none of the calves manifested local reactions at the injection site. Onset of immunity was therefore supported to start from 15 days after completion of the initial vaccination scheme in this homologous challenge model. The homologous challenge model was accepted for this emergency vaccine.

Study of the efficacy of ZULVAC 1 Bovis batch reference

This study aimed to evaluate the efficacy of ZULVAC 1 Bovis, in order to test if the vaccine was able to prevent viraemia (presence of viral genome in the blood) in 100% of the vaccinated and challenged calves. Three groups of calves were made. Calves in groups 1 and 2 were vaccinated and revaccinated after three weeks with two different BTV-1 vaccines. Twenty-one days after revaccination calves from all groups were challenged with BTV-1. 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.). Blood samples were taken on D0 and D42 (prior to challenge) and serological responses measured by ELISA and SN. 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 the presence of the BTV genome with the real time RT-PCR technique. The animals were monitored on days 0, 3, 5, 7, 10, 13, 17, 20, 24 and 27 post infection 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 none of the calves showed any systemic reactions neither after the first nor the second injection. Serological response after vaccination was detected both as ELISA and SN titres. Rectal temperatures were significantly increased in controls compared to vaccinates on day 7 post infection (day of maximal viraemia). However the rectal temperature increase in the controls was very slight. Clinical signs after BTV-1 were observed in 2 vaccinated calves, but the symptoms were rather mild. Viral genome was not detected (RT-PCR) in any of the vaccinated calves, in groups 1 and 2 groups during 27 days after challenge with BTV serotype 1, whereas in all unvaccinated calves challenged (group 3), the viral genome was detected from day 3 after challenge. Prevention of viraemia was therefore demonstrated and the claim in the SPC, section 4.2 supported.

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

Study to verify if the ZULVAC 1 Bovis vaccine was able to prevent viraemia in calves vaccinated and challenged 1 year post vaccination

This study was conducted to verify if the ZULVAC 1 Bovis vaccine was able to prevent viraemia (no detection of viral genome by real time RT-PCR technique during 27 days post challenge) in calves vaccinated and challenged 1 year post vaccination. A group of calves (2.5 to 4 months of age and negative for antibodies to Bluetongue) was split in two. In group 1, calves were vaccinated and revaccinated after 3 weeks and in group 2, calves served as non-vaccinated controls. A percentage of them were challenged with BTV-1 at an age of 15-16 months of age. Each group was intramuscularly (i.m.) injected with a 2 ml dose of the corresponding vaccine preparation. After each vaccination, the calves were monitored for the appearance of any systemic reaction associated with the vaccine administration (anaphylactic shock, anorexia, vomiting, etc.). Blood samples were taken from the calves: At D<0 (before 1st vaccination), D+18 (before 2nd vaccination), D+35, D+42, D+88, D+113, D+170, D+192/198, D+227, D+249, D+297 and D+331. On day D+373, an equal number of calves of each group were challenged with BTV-1. At 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 the presence of the BTV genome by the real time RT-PCR technique. The animals were also monitored on these days post infection for the appearance of clinical signs associated with the disease (rectal temperature, nasal and/or ocular discharge, nasal and/or ocular oedema, other oedemas, lameness and prostration).

Results showed that none of the calves manifested any systemic reactions (anaphylactic shocks and/or vomiting) after 1 st and 2 nd vaccinations. All calves were sero-negative to BTV-1 at D0. Before the challenge none of the calves (vaccinated and control) presented viraemia (blood sample). In none of the vaccinated calves (group 1) challenged with BTV serotype 1, viral genome was detected by real time RT-PCR during 27 days after challenge whereas in all the non-vaccinated (group 2) and challenged calves, the viral genome was detected from D+5 post inoculation. The experimental infections induced in calves were mild with non-specific clinical signs; however on day 7 post infection. control animals presented a higher rectal temperature than the vaccinated. Duration of 12 months was supported for this emergency vaccine.

Field trials

Efficacy data from field studies were not provided. According to the CVMP guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue disease, specific field trials are not a required.

Overall conclusion on efficacy

The efficacy data provided are considered sufficient to support the proposed indication for the active immunisation to protect cattle from 2.5 months of age against BTV serotype 1 infection and to prevent viraemia. The onset of immunity is 15 days after completion of the primary vaccination course, and duration of immunity is 12 months. Laboratory efficacy trials supported this claim.

In the absence of any specific data, and consistent with the approach followed for other ZULVAC BTV serotype monovalent and bivalent vaccines, the following statement was agreed to be used: 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

Introduction

ZULVAC 1 Bovis is a conventionally produced, liquid and ready-to-use, binary ethylenimine (BEI) inactivated, and aluminium hydroxide/saponin adjuvanted vaccine against bluetongue virus (BTV) serotype 1 infection.

Direct therapeutic benefit

The benefit of the product is prophylactic immunisation to protect cattle from 2.5 months of age against infection with BTV serotype 1. 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 15 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 (active immunisation and prevention of viraemia), there is a benefit to herd health both locally and regionally.

The use of vaccines such as ZULVAC 1 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, the starting materials which can be affected by extraneous agents or contaminants. This risk is mitigated by the control of the production process and starting materials to ensure no contaminants are present and that all in-process and final product tests are fully validated and that a validated inactivation process is used.

Secondly, the adverse reactions in the target animal in response to vaccination. There are limited local reactions after vaccination, and these are appropriately indicated in the SPC. 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 BTV vaccines. Safety studies demonstrate that the product is safe in both minimum age animals and also in pregnant animals.

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

According to the risk assessment provided, the active ingredient and excipients do not present a risk to the user.

The environmental risk assessment provided, demonstrates that Zulvac 1 Bovis contains no ingredients which are consider harmful to the environment.

Any risk to the consumer with respect to vaccines given to food producing species relate to any residual live organism or vaccines residues in meat. As ZULVAC 1 Bovis is inactivated there are no risks of residual live virus. With respect to residues from vaccination, it has been demonstrated that there are no residues left in meat which would present a risk to the consumer.

Conclusion on benefit risk balance

The information provided in the dossier (quality, safety and efficacy) and in response to points raised is sufficient to confirm an overall positive benefit risk balance under exceptional circumstances. No significant risks were identified when the product is used as indicated in SPC and under normal veterinary practice conditions. This conclusion is also supported by the experience gained from the positive outcome of the authorisation process of the two monovalent vaccines ZULVAC 8 Ovis/Bovis.

ZULVAC 1 Bovis has shown to be efficacious for the active immunisation of cattle from 2.5 months of age for the prevention of viraemia caused by BTV-1. Onset and duration of immunity is at 15 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 serotype 1 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:

- that 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;
- that Bluetongue disease is epizootic in nature and has the potential to result in high morbidity in susceptible populations;
- that there is a remaining epidemiological risk from Bluetongue serotype 1 (BTV1) for European bovine populations, in view of recent and previous outbreaks of BTV1 in Europe that constitute an objective need to have authorised products available for use in the coming months;
- 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 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 the applicant has agreed to the necessary specific obligations, to assure the safe use of the product in the field.

The applicant cannot reasonably be expected to provide the results from certain trials on the target species due to the difficulties in conducting large scale trials for a disease that is under Community control and the need for any experimental studies to be conducted within high containment facilities.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.