16 February 2017
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Zulvac BTV Ovis (EMEA/V/C/004185/0000)

Common name: bluetongue vaccine (inactivated)

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

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Introduction

On 2 October 2015 the applicant Zoetis Belgium SA submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Zulvac BTV Ovis, through the centralised procedure falling within Article 3(2)b of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 12 March 2015 as the applicant showed that this immunological veterinary product is intended for the treatment of an animal disease that is subject to Community prophylactic measures.

The rapporteur appointed is Noemi Garcia del Blanco and the co-rapporteur is Frédéric Klein.

Zulvac BTV Ovis is a multi-strain dossier application for sheep containing bluetongue virus (BTV), serotypes 1, 4 or 8 as the active substance. Zulvac BTV Ovis can be formulated to contain up to 1 BTV serotype. The applicant applied for the following indications: active immunisation of sheep from 6 weeks of age for the prevention of viraemia caused by BTV serotypes 1 or 8 and for the active immunisation of sheep from 6 weeks of age for a reduction of viraemia caused by BTV serotype 4.

The vaccine is presented as a suspension for injection and administered as a 2ml dose. It is filled into high density polyethylene (HDPE) vials of 10, 50 and 120 doses with a claimed shelf-life of 1 year.

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

On 16 February 2017, the CVMP adopted an opinion and CVMP assessment report.

On 25 April 2017, the European Commission adopted a Commission Decision granting the marketing authorisation for Zulvac BTV Ovis.

Scientific advice

Not applicable.

MUMS Status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the pharmacovigilance system (DDPS), version 1.4 dated 18 March 2015, in Annex 5.20, which fulfils the requirements of Directive 2001/82/EC, as amended. A statement signed by the applicant and the qualified person for pharmacovigilance (QPPV), indicating that the applicant has the services of a qualified person responsible for pharmacovigilance (PhV) and the necessary means for the notification of any adverse event occurring either in the Community or in a third country, has been provided.

Manufacturing authorisations and inspection status

The manufacture of the active substance and the finished product, including all packaging, and batch release is carried out by Zoetis Manufacturing & Research Spain S.L. (Spain). The site is routinely inspected by EU regulatory authorities and has been inspected within the last three years and a valid

Good Manufacturing Practice (GMP) certificate is available. No additional inspections specific to this vaccine are considered necessary.

Overall conclusions on administrative particulars

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

Part 2 - Quality

Composition

The vaccine may contain one of the following inactivated bluetongue virus strain antigens at concentrations equivalent to RP per dose (RP=relative potency by a mice potency test compared to a reference vaccine that was shown efficacious in sheep) as follows:

Bluetongue virus, serotype 1, strain BTV-1/ALG2006/01 E1: RP ≥ 1 (at release and end of shelf life)

Bluetongue virus, serotype 8, strain BTV-8/BEL2006/02: RP ≥ 1 (at release and end of shelf life)

Bluetongue virus, serotype 4, strain SPA-1/2004: RP ≥ 1 (at release) and RP ≥ 0.8 (at end of shelf life)

The vaccine contains aluminium hydroxide and *Quillaja saponaria* saponin extract (Quil A) as adjuvants, thiomersal as preservative as well as other excipients including sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections.

Container

The vaccine is filled into high-density polyethylene bottles closed with chlorobutyl elastomer stoppers and subsequently sealed with an aluminium cap. The bottles and stoppers all meet pharmacopoeial standards.

Development pharmaceutics

Zulvac BTV Ovis has been developed in accordance with the multi-strain dossier concept introduced in the revised Annex I to Directive 2001/82/EC. The three strains of BTV that may be incorporated into the finished product depending on epidemiological need have been selected based on expert advice and considering the 2015 epidemiological situation of bluetongue disease in the EU. Whilst the inclusion of the strains in principle is in line with the CVMP Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), bluetongue (BT) and Foot-and-mouth disease (FMD) (EMA/CVMP/IWP/105506/2007) it appears the product has not been developed in terms of being a flexible combination of 2 (or 3) of the 3 proposed strains. The potential cross-reactions between strains have not been investigated and, consequently, only monovalent vaccines can be formulated under the current multi-strain dossier. The vaccine is adjuvanted with aluminium hydroxide and *Quillaja saponaria* saponin extract (Quil A) selected for its ability to stimulate immunity whilst keeping an acceptable safety profile in the target species.

The target quantities of each of the respective antigens per dose have been determined on the basis of the results of a number of safety and efficacy studies carried out in the target species both with mono-antigenic vaccines and bivalent vaccines.

The vaccine contains thiomersal intended to minimise the risk of contamination and degradation of the vaccine during the use of multi-dose containers.

Method of manufacture

The vaccine is manufactured by a fairly standard procedure which is identical for all the three different BTV strains. The BTV strains are cultured in baby hamster kidney cells (BHK-21) either in roller bottles or bioreactors and inactivated by treatment with binary ethylenimine (BEI). After inactivation, the residual inactivant is neutralised with sodium thiosulphate. Antigen bulks can be stored at 2 °C – 8 °C for a maximum of 12 months. Data to support the storage of the bulk antigen for this period of time have been presented.

To formulate the finished product, the selected BTV inactivated antigen is mixed with the adjuvants and excipients. Maximum and minimum antigen inputs at formulation for each of the BTV antigens have been established based on the safety and efficacy studies. The calculation of the antigen input is based on virus titres pre-inactivation taking into account the dilution factor after inactivation and neutralisation. A blending table which can be applicable to any batch of monovalent vaccine is provided.

In general the method of manufacture is adequate.

Control of starting materials

Active substance

Detailed specifications have been provided for all starting materials used to manufacture the vaccine. The BHK-21 cell line and the various BTV master seeds are adequately tested to demonstrate freedom from extraneous viruses. New identity tests, based on RT-PCR and specific for each of the three BTV serotypes included in the vaccine, has been introduced to confirm the identity of BTV master and working seeds.

Excipients

The aluminium hydroxide used as adjuvant complies with Ph. Eur. monograph 1664. The adjuvant Quil A is not listed in a pharmacopoeia but its quality standard is satisfactory. All of the other excipients (thiomersal, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections) comply with respective Ph. Eur. monographs.

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

All of the starting materials of animal origin have been assessed and considered to be in compliance with the Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathies (TSE) agents via human and veterinary medicinal products (EMA/410/01 rev.3). The overall TSE risk associated with the inactivated vaccine is considered negligible.

Control tests during production

Control tests carried out during antigen production include virus titration, presence of sodium thiosulphate (to confirm complete neutralisation of the inactivant), residual live virus (inactivation), identity of BTV serotype and bacterial and fungal sterility. Validation of in-process tests is satisfactory.

Control tests on the finished product

The description of the following methods used for the control of the finished product is provided: appearance, volume, identity, *in vivo* potency, identification and quantification of the adjuvant aluminium hydroxide, thiomersal, sterility and pH. Appropriate specifications for each of the tests have been set.

Potential cross-reactions between strains have not been investigated so it is not possible to use a single potency test that is valid for all the strains included in the multi-strain dossier. For this reason, an individual potency test is carried out for each of the monovalent vaccines that can be formulated within this multi-strain dossier (monovalent BTV-1, monovalent BTV-8 and monovalent BTV-4).

The identification of the active substance in the finished product for each monovalent vaccine is confirmed in the antigen bulk before blending using the same specific RT-PCR techniques applied to the BTV master and working seeds.

The potency of the finished product was initially demonstrated for each monovalent vaccine in separate vaccination-challenge tests in transgenic mice where clinical signs (BTV-4) or mortality (BTV-1 and BTV-8) are used as end points for the evaluation of potency which is done by comparison with a reference vaccine. Validation of the potency tests for each monovalent BTV-1 and monovalent BTV-8 vaccines was already assessed and accepted during the corresponding centralised procedures. Validation data for the monovalent BTV-4 vaccine has been presented in the current dossier and it is considered sufficiently supported. The procedures for monitoring performance and replacement of reference vaccines and challenge stocks have been adequately described.

The applicant is currently working in the development of an *in vitro* test that could replace the current *in vivo* methods but such a test is not yet available. Some changes were proposed to be introduced to the current potency tests in order to refine (use more humane end-points) and reduce the number of mice used for potency testing. These changes included: change in the current end point for determination of potency from prevention of mortality to prevention of clinical signs, elimination of the sub-standard vaccine group included in the potency tests for BTV-1 monovalent vaccine and replacement of the potency for the monovalent BTV-1 vaccine for sheep by that used the monovalent BTV-1 vaccine for cattle. The proposed changes have been considered sufficiently supported by the data presented.

Overall, sufficient data have been provided to demonstrate that each of the potency tests, as originally performed, will be able to discriminate between standard and sub-standard batches of vaccine so that only potent batches of vaccines will be released to the market.

Limited data are currently available to support consistent production of BTV-8 or BTV-4 finished product using only BTV antigens manufactured in bioreactors. The applicant has proposed to provide data for three additional batches of monovalent BTV-4 formulated with antigens manufactured in bioreactors only. This is considered acceptable.

Stability

Stability data have been presented for the first virus passages that can be frozen and used for the initiation of other production runs. The data presented is supportive of the proposed storage period of 24 months at -70 °C ± 10 °C.

Stability data have been presented for the bulk antigens of BTV-1 and BTV-8. The data presented is supportive of the proposed storage period of 12 months at +2 °C to +8 °C.

The stability of the finished product has been demonstrated using batches of vaccine of bivalent BTV-1+ BTV-8 vaccine. The data presented is supportive of the proposed storage period of 12 months at +2 °C to

+8 °C. However, no data is currently available to support either the stability of inactivated BTV-4 antigens or the stability of the monovalent BTV-4 vaccine. Consequently, the shelf life of 12 months at +2 °C to +8 °C for all the possible monovalent combinations in Zulvac BTV Ovis is granted at this stage subject to the condition that additional real-time stability studies are carried out on three batches of vaccine containing only BTV-4 strain. The test results should be provided on an ongoing basis. The efficacy of the antimicrobial preservative was satisfactorily demonstrated.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls, and stability are provided in this part of the dossier.

The production methods as well as the in-process and final product quality control are appropriate to ensure the compliance with the specifications and a reproducible and consistent quality of the vaccine. The production process is described in sufficient detail to give confidence that the manufacture will yield a safe and effective vaccine of consistent quality and adequate stability suitable for the expected use of the vaccine in the EU.

Compliance of starting materials of animal origin used during production with the requirements of the Note for guidance on minimising risk of transmitting animal spongiform encephalopathy agents via human and veterinary products (EMA/410/01 rev.3) was shown.

In-process controls during manufacture and control tests on the finished product are appropriate to ensure the compliance with the quality specifications mentioned. Acceptance limits are properly established.

The applicant's proposal to set an end of shelf life specification of RP ≥0.8 for the monovalent BTV-4 was accepted based on the demonstration of a 15-month duration of immunity with a vaccine batch containing a lower antigen content than the minimum antigen content to be added at formulation of the monovalent BTV-4 vaccine and the similar levels of seroneutralising antibodies observed at onset of the immunity for vaccines at RP=1 and RP=0.8. Consequently, the specifications for the monovalent BTV-4 vaccine are RP ≥ 1 at release and RP ≥ 0.8 at the end of shelf life.

Limited data are currently available to support consistent production of BTV-8 or BTV-4 finished product using only BTV antigens manufactured in bioreactors.

A shelf life of 12 months for all the possible strain monovalent combinations in Zulvac BTV Ovis can be granted at this stage subject to the condition that additional real-time stability studies are carried out on three batches of vaccine containing only BTV-4 strain and the provision of results is made on an ongoing basis.

Overall, it is considered that the presented analytical dossier is adequate and sufficiently detailed to give confidence that the finished product is produced according to a consistent procedure of adequate standards and including adequate controls. Confirmation of the consistency of production in bioreactors and the stability of the monovalent BTV-4 vaccine will be addressed by post-authorisation conditions. This is considered acceptable.

The applicant should provide the following information as a post-authorisation condition:

- Stability results of three batches of monovalent BTV-4 on an ongoing basis. This is line with the requirements of the multi-strain dossier guideline EMA/CVMP/IWP/105506/2007.
- Data for three additional batches of monovalent BTV-4 formulated with antigens manufactured in bioreactors only.

Part 3 – Safety

Safety documentation

Nine safety studies have been carried out in compliance with the recommendations given in the CVMP Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), bluetongue (BT) and Foot-and-mouth disease (FMD) (EMA/CVMP/IWP/105506/2007). The safety studies have been carried out in the most sensitive category of the target species using the recommended route of administration with batches of vaccine manufactured to contain two BTV strains (bivalent vaccines) which were manufactured according to the dossier except for the inclusion of two different BTV strains, instead of one. Nevertheless, this can be considered as a worst-case scenario for the evaluation of safety of the monovalent vaccines included in Zulvac BTV Ovis. The maximum amount of a single BTV antigen to be included in the vaccine is ($10^{8.1}$ $TCID_{50}$/dose).

The laboratory safety studies presented in support of the safety of Zulvac BTV Ovis include: safety of the administration of a single dose and a repeated dose in lambs, and safety of an overdose in lambs. Six studies were also carried out in pregnant ewes for the examination of the reproductive performance.

No field safety trials have been performed; this has been justified based on the experience gathered from the use of the currently authorised bluetongue vaccines. Pharmacovigilance data available for the currently authorised vaccines (Zulvac 1 Ovis, Zulvac 8 Ovis, Zulvac 1+8 Ovis and Zulvac 4) have been provided together with the results of a post-authorisation field study carried out with Zulvac 1+8 Ovis which are overall supportive of the safety profile observed in the laboratory studies. The justification for not carrying out additional safety field trials is acceptable.

Laboratory tests

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

The safety of the administration of one dose and the repeated administration of one dose was investigated under laboratory conditions in one Good Laboratory Practice (GLP)-compliant study in which 13 lambs of the minimum recommended age were vaccinated with a total of three doses of vaccine administered, each three weeks apart, by the recommended route of administration. Seven lambs were inoculated at the same time with a placebo. After vaccination, no systemic reactions or alteration on the health status were observed. Transient increases in rectal temperature were very commonly observed during 24 hours after second and third vaccination with a maximum average increase of 1.19 °C with respect to the control group. Rectal temperatures returned to normal 24 hours later. Local reactions at the injection site appeared in all vaccinated lambs after the first and second vaccination, and in 92% after the third vaccination. Local reactions varied from: generalised diffuse swellings persisting for approximately 1 to 9 days or palpable nodular swelling of ≥ 2 cm in diameter that gradually decreased to nodules of smaller diameter (≤ 0.5 cm in the 54 - 61% of the lambs) that persisted in some cases for at least 48 days. The average duration of the local reactions was 30 to 44 days. The lesions at the injection site correspond to subcutaneous granulomas as determined by histopathology.

An additional GLP safety study was carried out under laboratory conditions in lambs of the minimum recommended age in order to support the safety of the repeated administration of one dose at a higher maximum antigen content. In this study, 8 lambs were vaccinated with a total of three doses of vaccine (bivalent BTV-1 + BTV-4 containing $10^{7.3}$ BTV-1 $TCID_{50}$ /2mL dose and $10^{8.0}$ BTV-4 $TCID_{50}$/2 mL dose) administered each two weeks apart. Eight lambs were inoculated at the same time with a saline. After

vaccination, no systemic reactions or alteration on the health status were observed. Transient increases in rectal temperature were very commonly observed in 24 hours after vaccination generally returning to normal values on the following days. The maximum individual rectal temperature increase observed after vaccination was 1.41 °C. Rectal temperatures generally returned to normal 24 hours later. Local reactions at the injection site developed in 88%, 100% and 63% of the vaccinated lambs after the first, second and third vaccination, respectively. Injection site reactions were visible (swellings) and palpable but in general not sensitive to palpation. The size of the reactions increased with the number of vaccines administered (maximum size: 59.9 cm^2 after the third vaccination) After vaccination, local reactions decreased in size gradually but were still present at the end of the study (maximum duration of lesions 60 days). Histopathology analysis of the injection sites revealed lesions consistent with subcutaneous fibrosis and granuloma in the vaccinated animals. In conclusion, results showed that the administration of a single and of Zulvac BTV Ovis and of the repeated administration of one dose of the vaccine is considered safe. Adverse reactions such as local reactions and transient increase in temperature are adequately addressed in the SPC.

Safety of one administration of an overdose

Although it is not currently a requirement for inactivated vaccines, the safety of an overdose of vaccine was studied in the GLP-compliant laboratory study in which 13 lambs of the minimum recommended age were administered with an double dose of vaccine (4 ml) administered by the recommended route of administration. Seven lambs were inoculated at the same time with a placebo. After the administration of an overdose, the adverse reactions were very similar to those observed after the administration of one single dose and the repeated administration of one dose. Likewise, no systemic reactions were observed after vaccination. Local reactions were present in 85% of the vaccinated lambs in form of small granules (diameter ≤ 0.5 cm) or oedema at the injection site which evolved into nodules (1 to 4 cm in diameter) or generalised oedema and then into small granules (diameter ≤ 0.5cm) that persisted for at least 48 days after injection.

In conclusion, results showed that the administration of an overdose of Zulvac BTV Ovis is considered safe. Adverse reactions are similar to those seen after administration of a single dose, however may persist for a longer time.

Examination of reproductive performance

The examination of the reproductive performance after vaccination was initially investigated in two different GLP-compliant laboratory studies in which pregnant ewes at different stages of gestation were administered with an overdose (double dose) of the vaccine administered by the recommended route. After vaccination, no systemic reactions were observed. In both studies, the reproductive parameters in the vaccinated ewes did not differ from those observed in the control ewes. In one of the studies carried out in pregnant ewes at 3-5 months of gestation, the rectal temperatures after vaccination were monitored. Vaccination induced a transient increase in the mean rectal temperature of 0.6 °C, with respect to the mean temperature of the control group, during the first 24 hours after vaccination. This result is consistent with the results of the safety studies in lambs. Local reactions were observed in 83% of the vaccinated ewes in form of nodular swellings of 1 to ≥ 2 cm in diameter (20% of ewes) or diffuse swellings (80% of the ewes). The local reactions may persist as small nodules of ≤ 0.5cm in diameter for more than 63 days. These two studies were not carried out following the recommended vaccination schedule, two vaccines doses administered within a 3-week interval, as per Ph. Eur. monograph 5.2.6.

In order to address the gap, four new GLP safety studies were carried out in pregnant ewes at the first half of gestation (2 studies) and at the second half of gestation (2 studies). At each stage of gestation,

reproductive performance and injection site reactions/rectal temperatures were evaluated in different studies. In all the studies, pregnant ewes were administered with two doses of a vaccine (bivalent BTV-1 + BTV-4 containing $10^{7.3}$ BTV-1 TCID50 /2mL dose and $10^{8.0}$ BTV-4 TCID50/2 mL dose) or placebo, three weeks apart. No abortions were observed in any of the studies and reproductive performance in the vaccinated pregnant ewes was normal. Vaccination induced a transient increase in rectal temperature peaking at 24 hours post-vaccination (maximum individual increase of 1.61 °C) and lasting for 24-48 hours. Local reactions at the injection site were observed in most of the vaccinated ewes and consisted of diffuse swellings evolving to nodules (maximum size: 36.5 cm^2) which may persist at least for 42 days. The results of these studies are supportive of the safety of the vaccine to pregnant ewes at first or second half of gestation.

The safety of the vaccine has not been investigated during lactation or in breeding males. Suitable warnings have been included in section 4.7 of the SPC.

The results of the safety studies have been adequately reflected in section 4.6 and section 4.10 of the SPC.

Examination of immunological functions.

No specific tests on immunological functions were carried out and this is considered acceptable because Zulvac BTV Ovis is a conventional inactivated vaccine containing classical compounds with no known adverse effect on immunological function.

Special requirements for live vaccines

Not applicable.

Study of residues

Not required.

The active substances being principles of biological origin intended to produce active immunity are not within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin.

The excipients, including adjuvants, are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The withdrawal period for Zulvac BTV Ovis is set at zero days.

Interactions

No specific studies have been conducted to investigate the interactions with other veterinary medicinal products and a statement to this effect is included in the SPC.

Field studies

No field safety data have been performed; this has been justified based on the experience gathered from the use of the currently authorised bluetongue vaccines. Pharmacovigilance data available have been provided together with the results of a post-authorisation field study which overall are supportive of the safety profile observed in the laboratory studies. The justification for not carrying out additional safety field trials is considered acceptable.

User safety

A user safety assessment has been conducted in accordance with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006). Due to the nature and concentration of its active substances (inactivated bluetongue virus – maximum one of the following BTV serotypes: BTV-1, BTV-8 or BTV-4) and other constituents, the vaccine does not pose any specific risk to the user when used as recommended.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with the CVMP Note for Guidance on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95).

Based on the data provided the ERA can stop at Phase I. Zulvac BTV Ovis is expected to pose a negligible risk for the environment when used according to the SPC.

The active substances are natural substances, the use of which will not alter the concentration or distribution of the substances in the environment.

Overall conclusions on the safety documentation

Overall, sufficient data were provided in order to evaluate the safety profile of Zulvac BTV Ovis when used in the target species according to the recommendations.

The results of the safety studies confirmed that the vaccine was generally well tolerated as demonstrated by the absence of major general reactions after vaccination. Vaccination may very frequently induce a transient increase in rectal temperature up to 1.6 °C may occur during the 48 hours following vaccination. Local reactions were acceptable in terms of size, frequency of occurrence and duration and consisted of diffuse swelling that persists for no longer than 7 days or palpable nodules up to a size of 60 cm^2 that decrease in size over time, occasionally persisting for more than 50 days. The results of the safety studies have been adequately reflected in the relevant sections of the SPC.

The safety of the vaccine in pregnant ewes was satisfactorily demonstrated; no impact of vaccination on the reproductive performance or on the offspring was observed. The safe use of the vaccine in breeding males or during laction was not investigated. Appropriate warnings have been included in the relevant section of the SPC.

Field safety studies were not conducted but this was suitably justified.

Zulvac BTV Ovis is a conventional inactivated vaccine containing active substances with no known adverse effect on immunological function. No specific residue studies were carried out but a withdrawal period of zero days has been justified.

No specific studies were conducted to investigate the interactions with other veterinary medicinal product. This is duly reflected in the relevant section of the SPC.

The risk of the vaccine to the end user and the environment is considered to be negligible when used as recommended.

To ensure comprehensive surveillance of the products and the serotypes administered to animals, it is recommended the applicant synchronises the periodic safety update report (PSUR) submissions for the multi-strain product together with the individually authorised products.

Part 4 – Efficacy

Introduction and general requirements

Zulvac BTV Ovis is a multi-strain dossier vaccine containing one out of three different serotypes of BTV (BTV-1, strain BTV-1/ALG2006/01 E1; BTV-8, strain BTV-8/BEL2006/02; or BTV-4, strain SPA-1/2004). These BTV serotypes are considered the most relevant to the current BTV epidemiological situation in the EU.

As acknowledged in the CVMP Guideline EMA/CVMP/IWP/105506/2007, efficacy cannot be demonstrated in the way usually required for other types of vaccines because of the number of possible combinations of antigens. This guideline indicates that mono-strain vaccines should be manufactured in compliance with the dossier for each available master seed viruses and efficacy should be shown for each of these mono-strain vaccines.

The efficacy studies presented in support of this multi-strain dossier were performed with the combinations of antigens that the applicant considers more relevant, these are: monovalent BTV-1, monovalent BTV-8, monovalent BTV-4 and bivalent BTV-1+8. Therefore, efficacy was studied for each of all the possible mono-strain vaccines in compliance with EMA/CVMP/IWP/105506/2007 and, furthermore, for a bivalent BTV-1+8 vaccine.

Laboratory trials

The onset and duration of immunity studies have been carried out in vaccination-challenge studies including animals of the minimum recommended age vaccinated according to the recommended schedule by the recommended route of administration, using batches of vaccine containing the minimum amount of antigen of each BTV strain to be used at formulation.

Determination of the dose

The minimum and maximum concentrations of each antigen (BTV-1, BTV-8 and BTV-4) per dose have been established based on the safety and efficacy studies included in Part 3 and Part 4 of the multi-strain dossier.

Four preliminary GLP-compliant immunogenicity studies have also been submitted to support the choice of vaccine dose. Three of these studies had been previously described in the dossiers for Zulvac 1+8 Ovis, Zulvac 8 Ovis and Zulvac 1 Ovis and there are no outstanding concerns. In addition, a preliminary immunogenicity study for Zulvac 4 has been presented. The studies are considered as supportive and a brief summary for each is included as follows:

In study, three different concentrations of the BTV serotype 1 were tested ($10^{6.93}$ $TCID_{50}$/dose; $10^{6.63}$ $TCID_{50}$/dose and $10^{6.33}$ $TCID_{50}$/dose, respectively). Three groups of 7 lambs (1-month-old; BTV seronegative) each were respectively vaccinated with one of the three experimental vaccines according to the recommended vaccination schedule. A group of 11 lambs were kept as non-vaccinated controls. The lambs were challenged 24 days after revaccination with 2 ml of virulent BTV, serotype 1 containing $10^{6.55}$ $TCID_{50}$/ml given by the subcutaneous route. The serological response, before and after vaccination, was evaluated by Enzyme-Linked Immunosorbent Assay (ELISA) and Serum Neutralisation (SN), respectively. Blood samples were collected at different times post challenge to evaluate the presence of virus by RT-PCR. Clinical signs were also recorded. The results showed that none of the vaccinated lambs developed viraemia during 28 days after challenge whereas all the control lambs were viraemic from day

3 post challenge. Rectal temperatures after challenge were significantly higher in control lambs. The three vaccines induced an immune response detected by ELISA and SN.

In study, four different concentrations of the BTV, serotype 8 were tested ($10^{7.3}$ $TCID_{50}$/dose; $10^{7.0}$ $TCID_{50}$/dose; $10^{6.7}$ $TCID_{50}$/dose and $10^{6.4}$ $TCID_{50}$/dose). Four groups of 12 lambs (1-month-old; BTV seronegative) each were respectively vaccinated with one of the four experimental vaccines according to the recommended vaccination schedule. A group of 12 lambs were kept as non-vaccinated controls. The lambs were challenged 25 days after revaccination with 2 ml of a virulent BTV, serotype 8 containing $10^{6.1}$ $TCID_{50}$/ml given by the subcutaneous route. The serological response, before and after vaccination, was evaluated by ELISA and SN respectively. Blood samples were collected at different times post challenge to evaluate the presence of virus by RT-PCR. Clinical signs were also recorded. The results showed that none of the vaccinated lambs developed viraemia during 27 days after challenge whereas all the control lambs were viraemic from day 5 post challenge. Rectal temperatures after challenge were not significantly different amongst groups.

In study, four different antigen concentrations of the BTV, serotype 1 and serotype 8 were tested ($10^{7.0}$ $TCID_{50}$/dose; $10^{6.7}$ $TCID_{50}$/dose; $10^{6.4}$ $TCID_{50}$/dose and $10^{6.1}$ $TCID_{50}$/dose of each serotype respectively). Four groups of 8 lambs (1.5-month-old; BTV seronegative) each were respectively vaccinated with one of the four experimental vaccines according to the recommended vaccination schedule. A group of 7 lambs were kept as non-vaccinated controls. At day 21 post revaccination, half of the lambs in each group were challenged with 2 ml of a virulent BTV, serotype 1 (strain BTV-1/ALG2006/01; containing $10^{6.5}$ $TCID_{50}$/ml) whilst the other half was challenged with 2 ml of a virulent BTV, serotype 8 (strain BEL2006/02; containing $10^{6.2}$ $TCID_{50}$/ml) given by the subcutaneous route. The serological response, before and after vaccination, was evaluated by ELISA and SN respectively. Blood samples were collected at different times post challenge to evaluate the presence of virus by RT-PCR. Clinical signs were also recorded. The results showed that none of the vaccinated lambs developed viraemia during 27 days after any of the different challenges whereas all the control lambs were viraemic from day 4 post challenge in both challenge groups. Rectal temperatures after challenge with BTV-1 or BTV-8 were significantly higher in the control group compared to the mean of the vaccinated group at some time points. Significant differences in clinical scores between vaccinated and control lambs were only observed after challenge with BTV-1 (day 8 post-challenge). The four vaccines induced an immune response detected by SN.

In study, two different concentrations of the BTV, serotype 4 were tested (3x $10^{6.0}$ $TCID_{50}$/dose and $10^{7.0}$ $TCID_{50}$/dose). Two groups of 7 and 10 lambs (1-month-old; BTV seronegative) were respectively vaccinated with one of the two experimental vaccines (K1 and K2) according to the recommended vaccination schedule. A group of 12 lambs were kept as non-vaccinated controls. Selected lambs (7 from K1 group, 5 from K2 group and 5 controls) were challenged 24 days after revaccination with 2 ml of a virulent BTV, serotype 4 (containing 2x$10^{7.0}$ $TCID_{50}$) given by the subcutaneous route. The serological response, before and after vaccination, was evaluated by ELISA and SN, respectively. Blood samples were collected at different times post challenge to evaluate the presence of virus by RT-PCR. Clinical signs were also recorded. The results showed that viraemia was reduced in both vaccinated groups. One lamb animal in group K1 showed inconclusive RT-PCR results at two consecutive time points whilst viraemia was not detected in any of the lambs in group K2 during 27 days after challenge. All the control lambs except one were viraemic from day 5 post challenge. Rectal temperatures after challenge were not significantly different amongst groups. The two vaccines induced an immune response detected by SN.

Onset of immunity

Four studies have been presented to support the onset of immunity (OOI) after vaccination. In each of this study, OOI was investigated using respectively a monovalent BTV-1 vaccine, a monovalent BTV-8 vaccine, a bivalent BTV-1+8 vaccine and a monovalent BTV-4 vaccine.

The OOI of a monovalent BTV-1 vaccine was investigated in a GLP-compliant laboratory study in which two groups of 14 lambs of the minimum recommended age (1.5 months of age), seronegative against BTV were vaccinated subcutaneously following the recommended schedule with a batch of vaccine containing the minimum antigen content fixed for the BTV-1 strain ($10^{6.4}$ $TCID_{50}$/dose) or with the same vaccine diluted (1:2) ($10^{6.1}$ $TCID_{50}$/dose). Eight lambs were kept as unvaccinated controls. A total of 12 lambs of each vaccinated group and six control animals were challenged 21 days after the completion of the vaccination scheme with a virulent homologous BTV-1 strain. The challenged animals were monitored for four weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature observed after challenge. No statistical difference in clinical signs was observed between vaccinated and control groups. Vaccinated animals developed an immune response of SN antibodies after vaccination with average titres at the time of challenge of 101.6 and 37.0 for each vaccinated group, respectively. In conclusion, this study is supportive of an OOI of 21 days for the monovalent BTV-1 vaccine formulated at a minimum antigenic dose proposed for this strain ($10^{6.4}$ $TCID_{50}$/dose) with an efficacy claim of prevention of viraemia.

The OOI of a monovalent BTV-8 vaccine was investigated in a GLP-compliant laboratory study in which three groups of ten lambs each, of the minimum recommended age, were vaccinated subcutaneously following the recommended schedule with a batch of vaccine containing either $10^{6.7}$ $TCID_{50}$/dose, $10^{6.4}$ $TCID_{50}$/dose or $10^{6.1}$ $TCID_{50}$/dose of the BTV-8 strain, respectively. Ten lambs were kept as unvaccinated controls. All the animals were challenged 44 days after the completion of the vaccination scheme with a virulent homologous BTV-8 strain. The challenged animals were monitored for four weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature after challenge. No difference in clinical signs was observed between vaccinated and control groups. Vaccinated animals developed an immune response of SN antibodies after vaccination with average titres being proportional to the antigenic dose of each vaccine. At 3 weeks after vaccination, average geometric titres were 53.8, 40.8 and 19.8, respectively. It can be concluded that the study is supportive of an OOI of 44 days after completion of the primary vaccination scheme for the monovalent BTV-8 vaccine formulated at a minimum proposed antigenic dose ($10^{6.5}$ $TCID_{50}$/dose of each antigen) with an efficacy claim of prevention of viraemia.

The OOI of a bivalent BTV-1+8 vaccine was investigated in a GLP-compliant laboratory study in which two groups of 33 lambs each were vaccinated subcutaneously according to the schedule with either a batch of vaccine containing $10^{6.7}$ $TCID_{50}$/dose of each BTV strain (group1) or with a vaccine containing $10^{6.5}$ $TCID_{50}$/dose (group 2) of each BTV strain. Thirty-three lambs were kept as unvaccinated controls (group 3). Three weeks after completion of the vaccination scheme, half of the lambs in each group were challenged with a homologous virulent BTV-1 strain and the other half with a homologous virulent BTV-8 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against

BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge with either of the BTV strains. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature and clinical signs after challenge with BTV-1. No differences in rectal temperature or clinical signs in the lambs challenged with BTV-8. In conclusion, the study is supportive of an OOI of 21 days after completion of the primary vaccination scheme for the bivalent BTV-1+8 vaccine formulated at a minimum proposed antigenic dose ($10^{6.5}$ $TCID_{50}$/dose) with an efficacy claim of prevention of viraemia.

The OOI of a monovalent BTV-4 vaccine was investigated in a laboratory study in which 12 lambs were vaccinated subcutaneously according to the schedule with a batch of vaccine containing $10^{7.2}$ $TCID_{50}$/dose of BTV-4 antigen. Eight lambs were kept as unvaccinated controls. Twenty-two days after completion of the vaccination scheme, all the lambs were challenged with a heterologous virulent BTV-4 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge. In contrast, all the unvaccinated control animals developed viraemia after challenge. Vaccinated animals developed an immune response of SN antibodies after vaccination with average titres at the time of challenge of 19.33. The results of this study are supportive of the proposed OOI of 21 days for the monovalent BTV-4 formulated at the proposed minimum antigenic dose of $10^{7.2}$ $TCID_{50}$/dose and the proposed efficacy claim of reduction of viraemia since complete prevention of viraemia was observed in the study.

Duration of immunity

Four different studies have been presented to support the duration of immunity (DOI) after vaccination. In each of this study, DOI was investigated using respectively a monovalent BTV-1 vaccine, a monovalent BTV-8 vaccine, a bivalent BTV-1+8 vaccine and a monovalent BTV-4 vaccine.

The DOI of a monovalent BTV-1 vaccine was investigated in a GLP-compliant laboratory study in which 40 lambs of the minimum recommended age were vaccinated subcutaneously following the recommended schedule with a batch of vaccine containing the minimum antigen content established for the BTV-1 strain ($10^{6.4}$ $TCID_{50}$/dose). Thirty lambs were kept as unvaccinated controls. A total of 20 vaccinated and 10 control animals were challenged 357 days (approximately 12 months) after the completion of the vaccination scheme with a virulent homologous BTV-1 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature after challenge. In conclusion, this study is supportive of 12-month DOI for the monovalent BTV-1 vaccine formulated at a minimum antigenic dose with an efficacy claim of prevention of viraemia.

The DOI of a monovalent BTV-8 vaccine was investigated in a laboratory study in which 33 and 34 lambs were vaccinated subcutaneously according to the schedule with a batch of vaccine containing, respectively, $10^{6.7}$ $TCID_{50}$/dose (group1) and $10^{6.5}$ $TCID_{50}$/dose (group 2) of BTV-8 antigen. Thirty-three (33) lambs were kept as unvaccinated controls. A total of twelve animals from group 1, 12 animals from group 2 and 12 controls were challenged 381 days (more than 12 months) after the completion of the vaccination scheme with a virulent homologous BTV-8 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that

viraemia was not detected in any of the vaccinated animals after challenge. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature after challenge. No difference in clinical signs was observed between vaccinated and control groups. In conclusion, this study is supportive of 12-month DOI for the monovalent BTV-8 vaccine formulated at a minimum antigenic dose ($10^{6.5}$ $TCID_{50}$/dose) with an efficacy claim of prevention of viraemia.

The DOI of a bivalent BTV-1+8 vaccine was investigated in a laboratory study in which 69 lambs were vaccinated subcutaneously according to the schedule with either a batch of vaccine containing $10^{6.7}$ $TCID_{50}$/dose of each BTV strain (group1) or with a vaccine containing $10^{6.5}$ $TCID_{50}$/dose (group 2) of each BTV strain. Sixty-eight lambs were kept as unvaccinated controls (group 3). Approximately 12 months (=366 days) after completion of the vaccination scheme, 30 animals of each group were challenged, half of them with a homologous virulent BTV-1 strain and the other half with an homologous virulent BTV-8 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. The results of the study showed that viraemia was not detected in any of the vaccinated animals after challenge with either of the BTV strains. In contrast, all the unvaccinated control animals developed viraemia after challenge. In addition, vaccination significantly reduced the rise of rectal temperature after challenge with either of the BTV strains. No difference in clinical signs was observed between vaccinated and control groups. In conclusion, this study is supportive of 12-month DOI for the bivalent BTV-1+8 vaccine formulated at a minimum antigenic dose ($10^{6.5}$ $TCID_{50}$/dose of each BTV-1 and BTV-8 strains) with an efficacy claim of prevention of viraemia.

The DOI of a monovalent BTV-4 vaccine was investigated in a GLP-compliant laboratory study in which 35 lambs were vaccinated subcutaneously according to the schedule with a batch of vaccine containing $10^{6.8}$ $TCID_{50}$/dose of BTV-4 antigen. Fifteen lambs were kept as unvaccinated controls. Approximately 15 months (=472 days) after completion of the vaccination scheme, 16 vaccinated and 8 control animals were challenged with a homologous virulent BTV-4 strain. The challenged animals were monitored for 4 weeks after challenge for the presence of viraemia (by real time RT-PCR), clinical signs associated to BTV infection and the presence of SN antibodies against BTV. After challenge, viraemia was observed in 19% of the vaccinated animals and in 100% of the control animals. In two vaccinated animals, viraemia was consistently observed during the observation period. Virus loads in the vaccinated animals were significant lower than those observed in the control animals. Very low levels of SN antibodies were observed in only 37.5% of the vaccinated lambs at challenge. Some deaths occurred in vaccinated and control animals, but these were not attributed to vaccination or challenge. The results of this study are supportive of 15-month DOI for the monovalent BTV-4 formulated at the proposed minimum antigenic dose of $10^{7.2}$ $TCID_{50}$/dose with an efficacy claim of reduction of viraemia.

Overall conclusion on efficacy claims, OOI and DOI

In line with recommendation EMA/43283/2010 and guideline EMA/CVMP/IWP/105506/2007, the proposal of the applicant to make a distinction in the SPC between the efficacy claim for BTV-1 and BTV-8 (prevention of viraemia) and the efficacy claim for BTV-4 (reduction of viraemia) is considered acceptable and relevant as it provides information about the level of efficacy that Zulvac BTV Ovis may induce depending on the specific BTV strain/s circulating in the field, which is relevant to the to the end user and/or Competent Authorities responsible for deciding on vaccination policies.

Different OOI and DOI have been proposed for the BTV serotypes 1 and 8 (OOI: 21 days; DOI: 12 months), and serotype 4 (OOI: 22 days; DOI: 15 months). Given the similarity in the OOI and DOI proposed for the different serotypes and in line with the recommendations in EMA/43283/2010), it is

suggested that the OOI and DOI are harmonised so there is only one OOI and DOI common for all the serotypes. Based on the efficacy data available, it is proposed that for all the BTV strains included in Zulvac BTV Ovis the OOI is harmonised to 21 days and the DOI is harmonised to 12 months, after the completion of the primary vaccination scheme.

The proposed annual revaccination scheme (i.e., one dose of 2 ml, every 12 months) for the monovalent BTV-1 and the monovalent BTV-8 are considered acceptable based on the results observed of an efficacy study where sheep receiving a booster vaccination 1 year post-primary vaccination course and challenged 21 days later did not developed viraemia. The serological response (SN antibodies) was similar to that observed after primary vaccination. For the monovalent BTV-4 vaccine, the revaccination schedule is two doses of 2 ml three weeks apart, every 12 months (equivalent to the primary vaccination course) as no data are available to support the efficacy of a single annual booster.

Effect of maternally-derived antibodies

The influence of maternally-derived antibodies on the efficacy of the vaccine has not been investigated. A standard warning has been included in section 4.4 of the SPC.

Field trials

No data on field trials have been provided. The absence of data from field studies based has been justified on the basis of the experience gathered so far with the respective monovalent and bivalent BTV vaccines that have been marketed in the EU in the recent years. The efficacy profile of these inactivated vaccines is considered satisfactory under field conditions.

Overall conclusion on efficacy

In line with the guideline EMA/CVMP/IWP/105506/2007, efficacy data have been provided for mono-strain vaccines containing each of the three different strains (serotypes) included in this multi-strain dossier for Zulvac BTV Ovis: BTV-1, BTV-8 and BTV-4. In addition, efficacy data have been generated using a bivalent vaccine containing two different BTV strains (BTV-1 and BTV-8). The number of strains to be included in Zulvac BTV Ovis has been restricted to one, therefore only monovalent vaccines will be marketed.

The efficacy of Zulvac BTV Ovis has been demonstrated under laboratory conditions using a vaccination-challenge model developed in the target species where sheep were vaccinated according to the recommended vaccination schedule and challenged with a virulent homologous BTV strain (except for the OOI study for BTV-4 where an heterologous BTV strain was used) after a defined period of time (21/22 days post vaccination for OOI and 12/15 months post vaccination for DOI). The relevance of the homologous challenge strains of the different serotypes and the heterologous BTV-4 challenge strain to the current epidemiological situation of BTV in the EU has been supported adequately.

It should be noted that the challenge strains used in the critical studies to support the prevention claims for serotypes 1 and 8 were homologous. The same level of protection may not be achieved following the incursion of a heterologous strain.

The primary variable to determine efficacy is the absence of detection of genome of BTV in blood samples collected after challenge using a validated RT-PCR which was shown to be specific for all BTV serotypes. Absence of viraemia has been defined as any RT-PCR result with a cycling value (Ct) ≥ 36. All the RT-PCR testing was carried out at the Spanish national laboratory for bluetongue except for one of the efficacy

studies for BTV-4 that was carried out at Zoetis-Spain. Validations of the RT-PCR techniques at the different sites, including the extraction method, have been provided and are considered satisfactory.

The onset and duration of immunity studies have been carried out including animals of the minimum recommended age (1.5 months of age) of the target species and using batches of vaccine containing the minimum amount of antigen of each BTV strain to be used at formulation.

An OOI of 21 days after completion of the primary vaccination scheme with a DOI of 12 months have been satisfactorily demonstrated for the monovalent vaccines containing BTV-1 or BTV-8. The efficacy claim supported by these studies is prevention of viraemia.

An OOI of 22 days after completion of the primary vaccination scheme with a DOI of 15 months have been satisfactorily demonstrated for the monovalent vaccines containing BTV-4. The efficacy claim supported by these studies is reduction of viraemia. According to the guidance EMA/43283/2010, the wording of the indications and warnings under section 4 of the SPC should be able to cover all strains/strain combinations. Should it be absolutely necessary to include a special indication or warning for a particular strain combination this should be clearly identified in the SPC. In line with the CVMP Guideline on data requirements for multi-strain dossiers for inactivated vaccine against avian influenza (AI), bluetongue (BT) and Foot-and-mouth disease (FMD) (EMA/CVMP/IWP/105506/2007), the efficacy claims supported by the studies should be reflected on the SPC as follows:

Active immunisation of sheep from 6 weeks of age for the prevention* of viraemia caused by bluetongue virus, serotypes 1 or 8.

Active immunisation of sheep from 6 weeks of age for the reduction* of viraemia caused by bluetongue virus, serotype 4.

* Below the level of detection of <3.9 $\log_{10}$ genome copies/ml by the validated RT-qPCR method, indicating no presence of viral genome.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: 12 months after completion of the primary vaccination scheme.

The influence of maternally-derived antibodies on the efficacy of the vaccine has not been investigated. A standard warning has been included in section 4.4 of the SPC.

The revaccination scheme for the monovalent vaccines containing BTV-1 or BTV-8 is one dose of 2 ml, every 12 months. For the monovalent vaccine containing BTV-4, the revaccination scheme consists of two doses of 2 ml three weeks apart, every 12 months. This is considered acceptable in the context of a multi-strain dossier.

No field data have been provided to supplement the results obtained in the laboratory studies. This has been justified based on the experience gained by the applicant from the field use of the respective monovalent and bivalent BTV vaccines which have been marketed in the EU in the recent years. The justification is acceptable.

Part 5 – Benefit-risk assessment

Introduction

Zulvac BTV Ovis is an inactivated, bluetongue vaccine consisting of 1 viral strain out of a set of 3 possible viral strains for BTV serotype 1, 4 or 8. It is a multi-strain dossier application which permits selection of relevant vaccine strains for formulation into a final vaccine in response to field need. Vaccines against

bluetongue virus (BTV) represent a special case in terms of the need for rapid and frequent change in the serotypes included in the vaccines. This is due to the unpredictability of the virus incursions and outbreaks of disease and the number of different serotypes of BTV that exist. The strains included are relevant to the current epidemiological situation of BTV in the EU. It is a full application under the multi-strain concept.

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

Benefit assessment

Direct therapeutic benefit

In well conducted laboratory studies, Zulvac BTV Ovis was shown to induce active immunisation in sheep from 6 weeks of age for the prevention of viraemia caused by bluetongue virus, serotypes 1 or 8, and the reduction of viraemia caused by bluetongue virus, serotype 4.

An overall onset of 21 days for all strains with duration of immunity for 12 months is shown.

Additional benefits

The ability to formulate the vaccine with a different strain (monovalent) gives flexibility to react to emergency situations.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The stability of the monovalent BTV-4 vaccine has not been confirmed. Limited data are currently available to support the production of BTV-8 or BTV-4 finished product using only BTV antigens manufactured in bioreactors.

Therefore the applicant should provide the following information as a post-authorisation condition:

- Stability results of three batches of monovalent BTV-4 on an ongoing basis. This is line with the requirements of the multi-strain dossier guideline EMA/CVMP/IWP/105506/2007.
- Data for three additional batches of monovalent BTV-4 formulated with antigens manufactured in bioreactors only.

For the target animal:

Vaccination may induce a transient increase in rectal temperature during the 48 hours following vaccination.

Vaccination may induce local reactions at the injection site in the form of diffuse swelling that persists for no longer than 7 days or palpable nodules up to a size of 60 cm^2 that decrease in size over time, occasionally persisting for more than 50 days.

No data on the efficacy of the vaccine in the presence of maternally derived antibodies or in seropositive animals have been presented.

The safety of the vaccine has been demonstrated in pregnant ewes, but not been evaluated during lactation or in breeding males.

For the user:

The potential risks to the person administering the product as well as other persons in direct contact with the animals have been evaluated in relation with the components of Zulvac BTV Ovis. The CVMP concluded that user safety profile for this product is acceptable when used according to the SPC recommendations.

For the environment:

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

For the consumer:

The adjuvants and excipients listed are either allowed substances for which table 1 of the Annex to Regulation (EU) No 37/2010 indicates that no MRLs are required or considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

Risk management or mitigation measures

Confirmation of the stability of the BTV-4 monovalent vaccines as well as confirmation of consistency of production in bioreactors will be provided as a post-authorisation condition.

No data on the efficacy of the vaccine in the presence of maternally derived antibodies or in seropositive animals have been presented. A suitable warning has been included in the SPC to mitigate this risk.

The safety of the vaccine has not been evaluated during lactation or in breeding males. A warning has been included in the SPC to mitigate the risk.

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

Evaluation of the benefit-risk balance

The product has been shown to be efficacious in preventing viraemia caused by bluetongue virus, serotype 1 and or serotype 8 and in reducing viraemia caused by bluetongue virus, serotype 4.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have satisfactory and uniform performance in clinical use. It is well tolerated by the target animals (sheep) and do not pose any relevant risk to users, environment and consumers when used as recommended.

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

Conclusion on benefit-risk balance

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Zulvac BTV Ovis is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore recommends the granting of the marketing authorisation for the above mentioned medicinal product.