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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of BTVPUR AlSap 1-8 (as published in December 2010). For information on changes after this date please refer to module 8.

1. Summary of the dossier

BTVPUR AlSap 1-8 is an aluminium hydroxide saponin adjuvanted vaccine intended for the active immunisation of sheep and cattle to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotype 1. The active substance of BTVPUR AlSap 1 is the inactivated bluetongue virus serotypes 1 and 8 (BTV1 and BTV8).

The benefit of BTVPUR AlSap 1-8 is the stimulation of active immunity in sheep and cattle against the bluetongue virus, serotypes 1 and 8. The vaccine dose is 1ml. The vaccination schedule consists of one injection given from 1 month of age, except in young animals born from vaccinated animals, in which case, vaccination should be delayed to 2.5 months of age. Onset and duration of immunity correspond to 3 weeks after the primary vaccination course.

Bluetongue Virus (BTV) can cause intense disease outbreaks in sheep. Fever is the most usual but not invariable clinical sign. If fever occurs sheep first become pyrexic 4-10 days after infection. The acute form in sheep is usually characterised by pyrexia up to 42°, depression, emaciation, ulceration of the oral cavity, swollen and sometimes cyanotic tongue, excessive licking movements of the tongue, lameness and abortion. Infection may result in the death of sheep within approximately 8-10 days or in a long recovery period with negative impact on the animals' welfare and growth. Mortality rate in sheep could reach up to 70% in a flock. BT is less common in cattle, some clinical signs have appeared in recent epizootic of in Northern West Europe caused by BTV 8 serotype, as well as infection caused by BTV 1 serotype in South of Europe. The most prominent lesions in BTV-1 infected cattle included nasal discharge, crusts/lesions of the nasal mucosa, salivation, fever, conjunctivitis, dysphagia, depression, congestions of the oral mucosa, redness of the skin, swollen teats and lameness.

Bluetongue serotype 1 has been responsible for outbreaks in the regions of Spain, Portugal and France, whereas, recent epidemics due to Bluetongue serotype 8 have occurred in several countries in Europe such as Belgium, Denmark, France, Germany, Luxembourg, The Netherlands, United Kingdom, Czech Republic, Switzerland, and also Austria, Italy, Spain, Sweden and Norway.

The dossier was reviewed in line with the provisions of Article 39(7) of Regulation (EC) No 726/2004 for an authorisation under exceptional circumstances and the recommendations 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).

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2. Quality assessment

Composition

The composition for one dose of 1 ml is provided in the following table

Names of ingredients		Quantity per 1 ml dose	Function	Reference to standards
Active ingredient	BTV1 antigen	≥ 8.1 CCID50(1)	Supply of antigen	Merial
Active ingredient	BTV8 antigen	≥ 7.1 CCID50(1)	Supply of antigen	Merial
Constituents of the adjuvant	Aluminium hydroxide	2.7 mg of Al^{3+}	Adjuvant	Merial
	Glycine buffer		Diluent of aluminium hydroxide	
	Purified Saponin		Adjuvant	Merial
Constituents of the excipient	Silicone antifoam		Antifoam	Merial
	Phosphate buffered Saline (PBS) buffer		Volume adjustment	Merial

(1) equivalent to titre prior to inactivation (log 10)

Container

The vaccine is filled in 100 ml and 50 ml capacity polypropylene bottles (Ph. Eur. 3.1.6) and in type I glass bottle (Ph. Eur. 3.2.1, 10 ml size presentation) closed with a butyl elastomer stopper (Ph. Eur. 3.2.9) and sealed with an aluminium cap. Tests of compliance with Ph. Eur. were provided and were found satisfactory.

Development Pharmaceutics

Choice of strains:

The BTV 1 strain was originated from an infected sheep during an outbreak in Pyrénées Atlantiques, France in 2007 and was selected for optimal antigen supply for an inactivated vaccine. The identity of the strain was confirmed by RT-PCR on the Master seed virus. The BTV1 was isolated and passaged first in embryonated specific pathogen free (SPF) hen's eggs, and finally was adapted to growth in BHKcells.

The BTV 8 strain was originated from an ill sheep during an outbreak in the Region of Ardennes, France in 2006 and was selected for optimal antigen supply for an inactivated vaccine. The identity of the strain was also confirmed by RT-PCR on the Master seed virus. As in the previous isolate, the BTV8 was isolated and passaged first in embryonated SPF hen's eggs, and finally was adapted to growth in BHK cells.

Manufacturing process:

The production is based on virus and cell lot systems. The Master seed virus of both isolated was constituted on BHKcells, and the Working seed virus was also expanded from it.

The vaccine antigens were produced in BHKcells, harvested and inactivated by a validated process. The inactivated virus suspension are filtered, concentrated, filtered again and purified by chromatograpy.

For the formulation of the vaccine classical adjuvants are used such as aluminium hydroxide and saponin, selected on the basis of the safety and efficacy demonstrated for similarly designed vaccines against BTV and FMDV produced by the applicant.

Establishment of minimum protective titre:

Within the framework of an "exceptional circumstance" application, the titre of each virus harvest just before inactivation was defined as the tool to quantify the active ingredients. To this aim, a limit of viral titre before inactivation of **>**8.1 $\log_{10}$ $CCID_{50}$/ml for BTV1 and > 7.1 $\log_{10}$ $CCID_{50}$/ml for BTV8 was set. In the frame of BTVPUR AlSap 1-8 registration, reference was provided of similar studies carried out using several experimental vaccine preparations containing different payloads of BTV1/BTV8 antigens. The antigen quality and quantity were monitored on several batches throughout the process using different analytical tools to assess the BTV1-8 consistency.

At routine industrial production level the vaccine is formulated to contain a defined equivalent quantity of non-concentrated virus culture for each serotype (the target volume was established based on the results of a series of efficacy studies performed with vaccine preparations containing varying payloads of different BTV serotypes, and by adding an extra safety margin to the minimum protective antigen content). This limit corresponds to the minimum protective antigen content. Moreover, a link between infectious titre prior to inactivation and protection was established. At blending, an infectious titre was defined for BTV1 and BTV8, ensuring the efficacy from batch to batch. The minimum virus titre was established for both antigens (corresponding to 8.1 CCID50/ml for BTV1 and to 7.1 CCDI50/ml for BTV 8 before inactivation).

For potency test, the challenge in target species (sheep) was chosen to assure good assessment of product qualities, because it directly reflects the efficacy of the vaccine.

Taking into account that the consistency of production was demonstrated under the specific manufacturing process of the current vaccine, the studies performed and considering the proposed batch potency test, the titer before inactivation can be considered acceptable under exceptional circumstances for the present application.

Validation studies

Inactivation kinetics

The results of the inactivation kinetics of a BTV1 and BTV8 suspension were provided in two of studies presented by the applicant (inactivation kinetics of BTV1 antigen) and (inactivation kinetics of BTV8 antigen) respectively in order to validate the inactivation processes reported in the dossier for the two active substances.

Considering that the slope of inactivation was quite abrupt and the fact that the inactivation is done in a two-step process undertaken in a strictly identical manner, a maximum limit of 9 log10 CCID50/ml was considered reasonable for both serotypes (BTV1 and BTV8).

The applicant presented other validation studies in order to validate different production processes of the finished product such as the validation of active ingredient BTV1 and BTV8 inactivation control tests, validation of the techniques for the titration of BTV1 and BTV8 and the validation of the quantification of specific protein by ELISA. The results of these studies were acceptable.

Composition of the batches used in the clinical trials

The data provided confirmed that all the experimental and production batches of the BTV active ingredient and finished product used in the safety and efficacy studies have been produced in the same manner. Safety and efficacy studies were carried out with the appropriate antigen payload and the production batches used in the safety and efficacy studies were representative of those proposed for commercial batches.

Method of manufacture

A detailed production flow chart for the finished product was provided. All stages of the manufacturing process were described in sufficient detail.

Unless specified (and in those cases appropriate GMP requirements are fulfilled) all the operations are conducted in closed circuits and all connections sterilised by means which are in compliance with Eur. Ph. such as steam and gamma radiation. The calculations of the volumes of the different components were described in sufficient detail. The final batches of the vaccine are formulated at a pre-defined fixed amount of volume of BTV 1 and BTV 8 virus culture.

Packaging

Primary packaging elements (bottles and closures) are sterilized by steam in compliance with the requirements of current Ph.Eur. Filling is carried out in clean atmosphere under laminar air flow of grade A located in an environment of grade B**.** All the bottles of vaccine coming from the same bulk and filled during the same cycle constitute a final lot. All the final lots prepared from the same bulk constitute a batch.

Control of starting materials

Starting materials listed in a pharmacopoeia

Details were provided for the following substances, and compliance with the relevant Eur. Ph. monograph was established with the provision of relevant certificates of analyses:

Starting material
Calcium chloride dihydrate
Disodium phosphate dihydrate
Formaldehyde solution (35%)
Magnesium chloride hexahydrate
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Sodium hydroxide
Water for injection

The provided information was acceptable.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Details, relevant control tests and certificates of analysis were provided for the following starting materials:

Starting material
BHKcells
BTV1 antigen
BTV8 antigen
Bovine serum
Casein hydrolysate
Porcine trypsin
Purified saponin

As a summary, the following information was included:

BHKcells: This cell line is a baby hamster kidney cell line used as a substrate for the production of both antigens.

Active substance:

BTV1 and BTV8 antigens: The origin and history of the virus strains were adequately explained. The isolates were first grown in SPF embryonated hen's eggs, and then adapted and grown in BHKcell line.

The Master seed virus (MSV) for both antigens were constituted after passage in BHKcells, and certificates of analysis were provided to demonstrate bacterial, fungal and mycoplasm sterility, viral purity, the identity of the virus strains (RT-PCR) and virus titer. The absence of viral contamination was checked by using general and specific tests.

The Working seed virus (WSV) for both antigens was stated to be obtained from no more than 3 passages from each MSV (also in BHKcells). Controls were carried out to demonstrate bacterial, fungal and mycoplasm sterility, identity (by RT-PCR) and the infectious titer.

Tests carried out on the (Master cell bank) MCB

In accordance with the Ph.Eur. general text and relevant EU guidance documents samples taken from homogeneous batch of MCB were tested for general examination of fibroblastic appearance during amplification, and for:

Bacteria and fungal sterility

- Mycoplasma sterility
- Extraneous agents. Absence of viral contamination was checked by using general and specific tests.
- Identification of species;
- Karyology (chromosomial analysis on MCB and MCB+20);

  In the Working Cell Bank (WCB) the same controls as for MCB were carried out with the exception of the identification of species and karyology

Starting materials of non-biological origin

Details of starting materials or components (e.g., glycine buffer, stabiliser F2 and PBS), preparation (if appropriate), relevant control tests and certificates of analysis were provided for the following substances:

Starting material	Used for preparation of/ function
Aluminium hydroxide	Vaccine (adjuvant formulation)
Bromoethylamine Hydrobromide (BEA)	BTV1/BTV8 (inactivating agent)
Chloroform	BTV1/BTV8 (stabilisation of AI)
Glycine buffer	Vaccine (preparation of adjuvant)
Hydrocloric acid (1M solution)	Vaccine (preparation of adjuvant)
Phosphate buffered Saline (PBS) buffer	Vaccine (diluent of the vaccine)
Stabiliser F2	BTV1/BTV8
Silicon antifoam	Vaccine (formulation of the vaccine)

The provided information was acceptable.

Excipients:

Details on aluminium hydroxide, glycine buffer and PBS were provided and were found in compliance with the relevant requirements.

In House preparation of media

Description of constituents, method of preparation, including sterilisation procedure carried out according to the requirements of current Ph. Eur., basic controls carried out during preparation have been provided to support the quality of the following media:

- GMEM,

- Virus Maintenance Medium.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (TSE)

The assessment of the starting materials was conducted in accordance with: the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products (EMEA/410/01-Rev.2), the Position Paper on the Assessment of the risk of transmission of animal spongiform encephalopathy agents via Master seed materials used in the production of veterinary vaccines the and Commission Directive 199/104/EEC, in order to demonstrate that the risk for transmission of TSE due to the starting materials used in the manufacturing of the vaccine is minimal.

BTV1 and BTV8

As mentioned earlier in the report, the origin and history of the virus strains were adequately supported. Also the analysis of the controls performed on MSV and WSV were presented in order to demonstrate the quality of both antigens.

The preparation of the active ingredient(s) was adequately explained, a flow chart was included and the consistency of the production was confirmed by the results obtained form different batches of active substance of BTV1and BTV 8.

The TSE negative status for both antigens was justified adequately. The certificate including the results of the tests performed and providing evidence of the TSE negative status of the sheep from which virus seed material was derived was provided.

Bovine serum: Assurance that the donor animals comply with the regulations concerning TSEs including specific and adequate EDQM certificates of suitability were provided. Purity tests and γ-irradiation are used as complementary measures to achieve a high security level against potential contamination, and validation of the irradiation method was provided.

Casein hydrolysate is manufactured from enzymatic (with a porcine enzyme collected from swine declared fit for human consumption) hydrolysis of bovine casein made from bovine milk sourced from healthy animals (in compliance with EU legislation on TSE) declared fit for human consumption; it is irradiated and adequate controls are performed to assess the quality of the product.

Porcine trypsin: is manufactured from pancreas of swine that are declared fit for human consumption; it is irradiated and adequate controls are performed to assess viral purity.

An assessment was conducted in order to demonstrate that the risk of transmission of TSE is significantly minimised by the documented and recorded sourcing of animals (animal-derived material of known and controlled origin), by the nature of animal tissues used in manufacturing (low or no detectable infectivity), by the production processes, and by the negligible risk posed as a series of factors would likely lower the risk if any, such as the high dilution of the materials used, the route of administration and maximum/minimum number of dosage injected. Adequate certifications of suitability or conformity of the materials used were provided as appropriate.

The CVMP concluded that 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

The following tests are performed during production:

- Checking of the sterilizing filter integrity (Ph. Eur. compliant)
- Monitoring of the sterilisation cycle (Ph. Eur. compliant)
- Temperature and Time recording

During secondary packaging (classical), the following in-process control tests are performed

- Checking of the filled volume
- Checking of the appearance of the product after capping
- Checking of the conformity of the product presentation (after packaging)

The above tests were described in detail and were found satisfactory.

Control tests on the finished product

The control tests on the finished products are summarised below. The methods, frequency and pass criteria for the tests were provided in details and were found acceptable.

General characteristics of the finished product

Test, Appearance, pH, Volume, Free Formaldehyde (FF)

Identification and assay of AI

Quantification: Viral content (titre before inactivation on each blend): The mean infective titre before inactivation per ml of bulk is calculated based on the infective titre of each Active Ingredient (AI) in the batch and their proportion in the blend.

Quantification: Antigen content (ELISA): (on each blend): The mean titre of a BTV1/BTV8 viral suspension per ml of bulk is calculated based on the titre of each Active Ingredient in the batch and their proportion in the blend.

Potency in sheep:

Susceptible sheep are vaccinated with one dose of the vaccine subcutaneously (s.c) and submitted to a virulent challenge 21-35 days after. In parallel other susceptible sheep are used as controls in order to check the antigen quantity by protection against challenge.

Identification and assay of adjuvants

Test, Aluminium hydroxide

Sterility and Purity tests

Test, Bacterial and fungal sterility

Safety test

Specific safety:

Sheep 3-6 months old are inoculated subcutaneously (s.c.) with 2x doses of the vaccine. Rectal temperature (T°), general reactions and local reactions are recorded. No abnormal local or general reaction must be observed during the period of observation.

Batch to batch consistency

Batch to batch consistency was shown as the applicant included results from three final lots of the current vaccine which were satisfactory in relation to production consistency.

Stability

No specific studies were carried to support the stability of BTVPUR AlSap 1-8. Due to similarities between vaccines of other BT serotypes, data obtained from other BT vaccines (BTV 2, BTV 4 and BTV 2-4) produced by the same company were extrapolated to support the stability of the vaccine under application.

As stated in the applicable Guideline on Minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue

(EMEA/CVMP/IWP/220193/2008), a maximum shelf life of **12 months** can be granted in the absence of data. Due to the need to provide authorised vaccines against Bluetongue serotypes 1 and 8 as soon as possible and the considerable time required in order to complete all stability studies in line with normal requirements the CVMP exceptionally accepted the current limited data with a view for the applicant to provide the remaining information as soon as available. The manufacturer therefore was requested to provide a full set of data to support the stability of the product for each presentation. The design and timelines of the studies were presented and considered acceptable.

OVERALL CONCLUSION ON QUALITY

At present, with the data and clarification provided by the manufacturer, the quality profile of BTVPUR AlSap 1-8 can be considered as sufficient for granting a marketing authorisation under exceptional circumstances when taking into account the benefit-risk balance for BTV1 and 8 serotypes, and when considering the epidemiological situation in the EU.

In this context given that:

- a batch with low antigen content was shown to be efficacious in both sheep and cattle,
- the production process allows production of consistent batches, with specifications on both "titre before inactivation" and "specifications of the challenge test on sheep" for both antigens,

the CVMP has sufficient guarantees to assume that forthcoming batches will be efficacious in both sheep and cattle when manufactured and released on the basis of the descriptions and specifications presented.

All these assurances were considered sufficient for granting a marketing authorisation under exceptional circumstances.

3. Safety assessment

Introduction and general requirements

BTVPUR ALSAP 1-8 is a conventionally produced, liquid and ready-to-use inactivated vaccine, adjuvanted by aluminium hydroxide and purified saponin. One-ml dose is recommended to be administered by subcutaneous route in sheep and cattle. The proposed basic vaccination schedule consists in both species of one injection in naïve animals from 1 month of age (or from 2.5 months of age in young animals born from vaccinated animals), followed by a second injection after 3-4 weeks. Onset of immunity is 3 weeks after primary vaccination course, and the duration of immunity is not yet established.

In light of the provisions in 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) safety tests with either representative experimental batches or standard production batches can be used. Batches containing higher antigen amounts (i.e. two times higher than the standard amount) were tested in submitted laboratory trials. The guideline allows also that data generated from other vaccines of similar composition (in terms of excipients and adjuvants) in the same or a similar range of target species can be used to fulfil safety requirements under exceptional circumstances. In the same document, field trials are not strictly required. Evidence of the safe use of BTV vaccines containing different BTV serotypes (e.g. BTV2, 4, 2&4 from field experiences in Corsica and Portugal) was shown. No additional data were provided in order to support the safety of the vaccine in animals of non-target ruminant species. The applicant presented results demonstrating

the safety of BTVPUR AlSap 1-8 vaccine in sheep and cattle mainly using production batches of vaccines formulated with different BTV serotypes antigen having a similar composition in adjuvants/excipients (BTV1-4, BTV2-4, BTV4-8 vaccines). One pivotal study was performed with a bivalent vaccine with had the same combination of serotypes as BTVPUR AlSap 1-8 (BTV1 and BTV8) All batches of vaccines used in the various safety trials were manufactured in accordance with the quality requirements presented in the analytical part of the dossier.

A. Safety assessment

Laboratory tests

A series of studies using bovalent vaccines with combinations such as BTV 2-4, BTV **1-8**, BTV 1-4 and BTV 4-8 vaccines, respectively were presented. Conventional, BTV-antibody free-animals were used for all studies.

The local and general tolerance to vaccination was studied after each administration of the vaccine.

The standard parameters used to support the safety profile of the vaccine are listed below:

- Clinical signs after vaccination
- Impact on body temperature (T°)
- Impact on growth performance (body weigth)
- Local reactions
- Post mortem examination (including selected investigation of injection site)
- Serology: BTV serotype specific SNT

Safety of the administration of one dose /an overdose/ a repeated administration of an (over)doses

In this report, only pivotal safety studies are presented to support the BTVPUR AlSap 1-8 safety. Other safety studies that were presented for the authorisation of the products BTVPUR ALSAP 2-4 and 8 from the same company were considered as supportive data only.

For the authorisation of BTVPUR ALSAP 1-8, the applicant presented two pivotal studies, performed with production batches, to support the safety of the product. The aim of both studies was to assess the safety of bivalent inactivated vaccines (BTV1-8, BTV 1-4, and BTV 4-8 with similar manufacturing process and composition) containing high antigen payloads in young lambs and calves (around 1 month of age)

SHEEP

Safety assessment of two BTV (Bluetongue Virus) bivalent inactivated vaccines BTV1-4 and BTV1-8 containing high antigens payload in one-month old lambs

Lambs of 1-months of age were randomised in three groups. One group was vaccinated with BTV **1-8**, the second group was vaccinated with BTV **1-4** and to the third group placebo was administered.

Each lamb received by the subcutaneous route on Day 0 (D0) 2 ml (2 x dose) of vaccine or placebo as appropriate for the group. On D 14 each lamb received by the subcutaneous (SC) route 1 ml (1 dose) of vaccine or placebo, and on D29 each lamb received the third dose of vaccine or placebo as appropriate for the group.

General reactions including clinical signs, rectal temperatures (T°) and body weight were measured.

Local reactions (including post-mortem examination) were measured and also serological examination (BTV serotype specific SNT) was performed.

Results from this study: no general systemic reactions were reported in vaccinated and control animals, except of a very rare and transient apathy in one vaccinated animal. There was a moderate and transient increase in rectal temperatures of vaccinated animals that was statistically significant after the second vaccination. No impact on body weight was observed.

Local reactions: moderate swelling reactions were observed after first and second vaccination. In the post-mortem observation it was a classical local subcutaneous lesion and disappears at the end of the observation period (D 49).

All lambs were seronegative to BTV1, BTV4 and BTV 8 before vaccination and a serological conversion was observed in the vaccinated animals after vaccination whereas the control group was seronegative.

Conclusions: The general safety of the vaccine was demonstrated in lambs of young age.

CATTLE

Safety assessment of a bivalent inactivated vaccines BTV-4/BTV-8 (Bluetongue virus serotype 4 and 8) vaccine containing high antigen payloads in young calves

Calves of 3-4 weeks of age were randomised in two groups. One group was vaccinated with a bivalent vaccine containing serotypes BTV **4-8**, and the second group were used as controls. In this group only placebo was administered.

Each calf received by subcutaneous route on D0 2 ml (2x dose) of vaccine or placebo as appropriate for the group. On D 14 and D 29 each calve received by subcutaneous (SC) route 1 ml (1 dose) of vaccine or placebo, as appropriate for the group.

General reactions including clinical signs, rectal temperatures and body weight were measured.

Local reactions (including post-mortem examination) were measured, and also serological examination was performed for BTV serotype specific seroneutralising (SNT) antibodies.

Results: no general systemic reactions were reported in vaccinated and controls, except of a rare and very transient apathy in one vaccinated animal and decrease of appetite in other animal one day after vaccination. There was a very moderate and transient increase in rectal temperatures of vaccinated animals following repeated dose. No impact on body weight was observed.

Local reactions: limited swelling reactions were observed, that disappeared within 4 weeks after vaccination, and in the post-mortem examination these lesions were granulomatous inflammatory reactions of very limited size in one third of the injection sites.

All calves were seronegative to BTV4 and BTV 8 before vaccination and a serological conversion was observed in the vaccinated animals after vaccination whereas the control group was seronegative.

Conclusions: The general safety of the vaccine was demonstrated in calves of young age.

Conclusions from both studies: The general safety of the vaccine was demonstrated in animals of the minimum age of both species. 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.

Examination of reproductive performance

Two studies were performed (one in sheep and one in cattle) using a bivalent vaccine which included serotypes 2 and 4:

SHEEP

Safety study of the bivalent vaccine BTV2/BTV4 with high antigens payload in pregnant ewes

Pregnant females were randomised in four groups as follows: Groups A and B: 7 weeks pregnancy stage; (vaccinated on D0 and controls) and Groups C and D: animals at 18 weeks pregnancy stage (vaccinated on D77 and controls).

One dose of vaccine (or 1 ml of placebo) was administered subcutaneously and from the day of vaccination to the day of lambing the animals were monitored

General reactions and rectal temperatures were measured during 4 days after vaccination or administration of placebo. The reproductive performance and growth of the lambs was also measured. Serological examination (BTV serotype specific SNT antibodies) was performed on D0 and D77 and at weaning.

Results: In this study no significant increases of rectal temperature or abnormal clinical signs were observed after the vaccination. No treatment-related impairment of the reproductive performance was reported. Because of that the safety of the vaccine in pregnant ewes was considered demonstrated.

CATTLE

Safety study of the bivalent vaccine BTV4/BTV8 with high antigens payload in pregnant cows.

A group of pregnant females (31-259 days of gestation) was randomised in two groups: Vaccinated and controls.

Two doses of vaccine (or placebo) were administered subcutaneously (SC) on D0 and D28 of the test and from the day of vaccination to the day of calving the animals were monitored.

General reactions and rectal temperatures were measured during 4 days after first and second vaccination or administration of placebo. The reproductive performance, health status of the offspring during the first 2 weeks of life and milk production during lactation was also measured. Serological examination (BTV serotype specific SNT) was performed on D0, D28 and at calving.

Results: In this study no significant increases of rectal temperature or abnormal clinical signs were observed after the vaccination. No treatment-related impairment of the reproductive performance was reported. No effect in the milk yield in the cows was reported. Because of that the safety of the vaccine in pregnant and lactating cows was considered to be demonstrated.
To note, a field BTV 8 infection occurred during this trial and almost all vaccinated and control cows were positive by ELISA showing that the BTV-8 infection had spread into the herd. The RT-PCR results showed that none of the vaccinated cows were viraemic while most of the controls were detected positive.

Although safety (and efficacy) studies were not performed in breeding males with BTV 1+8, its use has not been contraindicated in this specific category of animals but a warning is included in the product literature, recommending the use on these animals according to benefit/risk assessment performed by the responsible authorities.

Examination of immunological functions

No specific study was carried out as no negative influence on the immune response is expected due to the vaccination.

Interactions

As no specific studies were carried out, a recommendation for not mixing with other Immunological Veterinary Medicinal Products has been included in the SPC.

Field studies

Data from field studies were not provided. This is in line with the current requirements included in 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) where is stated that field studies may be omitted. The applicant could not reasonably be expected to provide the results from such 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.

In the dossier the applicant mentioned the safe use of BTV4 and/or BTV2&4 in Corsica, Spain, Portugal and Italy. In addition, the vaccine against serotype 8 from the same company has been also authorised and used in several European countries (Austria, Belgium, Denmark, France, Germany, Italy, Portugal, Sweden, Switzerland and United Kingdom). All these vaccines have shown good tolerance under field condition both in cattle and sheep. Proof of evidence for the safe use of the BTV-8 (BTVPUR AlSap 8) vaccine in sheep and cattle was given by the periodic safety report (PSUR) which was submitted by the applicant. The conclusion is that safety data of BTVPUR ALSAP 8 are consistent with the cumulative experience to date and with the approved label text.

B. Residue assessment

The vaccine contains an inactivated whole virus, a buffer solution and adjuvant. The latter consists of aluminium hydroxide, saponin and water for injection. No specific residues studies were considered necessary.

MRL

The active substance being a principle of biological origin intended to produce active immunity is not in the scope of Regulation (EC) 470/2009.

The excipients, including adjuvants, listed in section 6.1 of the SPC 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.

Withdrawal period

Sheep: Zero days

Cattle: Zero days

Environmental risk assessment

A phase I assessment was carried out, providing evidence that there would be no potential risk for the global environment. No phase II assessment was deemed necessary. No hazard should be posed to the environment in light of the nature of the vaccine, in particular of the antigen (inactivated) and the adjuvant(s). Additionally, no special concern is posed by the final product in light of the safety of packaging, of the limited number of injections and of the maximum quantity administered to animals, of the route and method of administration, and of the product's disposal. Consequence and level of risk are practically nil, thus justifying the absence of phase II assessment.

User safety

For the user there is a risk of self injection. Appropriate warnings and advice on the SPC have been included to reduce this risk.

Overall conclusions on safety

In general, sufficient data were provided in order to assess the potential risks arising from the use of BTVPUR AlSap 1-8 in the target animal species. The majority of safety data were extrapolated from the results obtained in laboratory studies aiming to demonstrate the safety of production batches of similar vaccines (e.g. containing different BTV serotypes and the same amount of adjuvants) administered subcutaneously in either single, repeated or (over)dose. However a pivotal study with the vaccine under application was provided.

Under the tested conditions, the vaccines were generally well tolerated as demonstrated by the absence of major systemic reactions impacting body temperature (T°) and growth performances following administration in sheep or cattle. Local reactions in sheep and cattle were acceptable in terms of size, frequency of occurrence, and duration. Studies regarding the reproductive performances were provided that were conducted on pregnant ewes and cows using similar bivalent vaccines in order to extrapolate conclusions; no impact on the offspring was reported. The safe use of the vaccine in breeding males was not demonstrated, nor the safe use in lactating sheep; both have been reflected in relevant sections of the SPC. Data from field trials were not provided, in line with current requirements. No specific residue studies were carried out but a withdrawal period of zero days has been justified. The consequence and level of risk arising from use of the vaccine are practically nil as per the conclusion from the phase I ecotoxicity assessment. No additional data were provided in order to support the safety of the vaccine in animals of non-target ruminant species.

Evidence was provided that showed that there is no potential risk for the environment. For the user there is a risk of self injection. Appropriate warnings and advice on the SPC were included to reduce this risk.

4. Efficacy assessment

Introduction and General Requirements

BTVPUR ALSAP 1-8 is a conventionally produced, liquid and ready-to-use inactivated vaccine, adjuvanted by aluminium hydroxide and purified saponin. Final batches are formulated to contain, in 1ml of dose of the vaccine, a fixed amount of volume of each virus culture and an amount of respectively, 2.7 mg Al^{3+} and 30 HU saponin. The product is indicated to prevent viraemia and to

reduce clinical signs in sheep and cattle caused by BTV serotype 1 and 8. A 1 ml dose of the current vaccine is recommended to be administered by subcutaneous route in animals of the target species. The vaccination schedule consists of one injection given from 1 month of age, except in young animals born from vaccinated animals, in which case, vaccination should be delayed to 2.5 months of age. Primary vaccination includes a second injection of 1 ml dose given 3-4 weeks after the initial injection. Onset of immunity is 3 weeks after primary vaccination course. Revaccinations consist of one yearly injection, but the duration of immunity is not yet established, and any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian (reflected in the relevant section of the SPC). Although (safety and) efficacy studies were not performed in breeding males, its use is not contraindicated in this category of target animal species.

To demonstrate the efficacy of the product, batches of vaccines with different BTV antigens have been used in the various efficacy trials. The batches were manufactured in accordance with the quality requirements presented in the analytical part of the dossier. Besides the nature of the BTV strain used no other changes were allowed, so the identity between products can support the use of data obtained from other vaccines. The majority of the qualities of the BTV vaccines are expected to remain consistent from one vaccine to another, including the efficacy and therefore studies done with other serotypes may be supportive of demonstration of efficacy for other BTVPUR AlSap vaccines.

The efficacy was demonstrated by virulent challenge and the measurement of viraemia through RT-PCR and clinical signs in vaccinated animals. The uptake of the vaccine was assessed through the analysis of the humoral immune response induced by each immunisation, as measured by titration in a sero-neutralisation assay against the same serotype(s) included in the vaccine preparations. No additional data were generated to demonstrate the efficacy in animals of non-target ruminant species. Field trials were not strictly required for this type of application. There are no specific efficacy field trials to support this authorisation. DIVA strategy for this vaccine has not been implemented.

Laboratory trials

Establishment of a Challenge Model

No specific study (neither in sheep nor in cattle) was carried out in order to validate a challenge model using the BTV1 or BTV8 serotypes. However, during preliminary studies performed by the applicant the effect of factors like virus dose, type of inoculum, route of inoculation, passages in cell cultures, etc. was evaluated in order to establish a valid challenge model.

For the laboratory efficacy trials, the following isolates were used:

- BTV1 challenge virus stock was produced from a BTV1 field isolate originating from Portugal in 2007.

- BTV8 field isolate was obtained from red blood cells (RBC) collected from infected sheep in Belgium in 2006

The diagnostics techniques used in the efficacy studies presented were serological techniques such as the sero-neutralisation assay and RT-PCR. The details and validation of these techniques were provided and were acceptable.

About the RT-PCR:

On the basis of the provided information and the answers given during the procedure it was concluded that the RT-PCR used for the detection of viremia in the efficacy studies was qualitatively and quantitatively validated. The Positive Threshold at 95% was set at 3.68 log10 RNA copies/ml (indicating no infectious virus transmission).

SHEEP

Assessment of protection against a BTV-1 challenge in sheep

Safety and efficacy study of four monovalent BTV-1 and one trivalent BTV1-4-8 vaccines formulated with different payloads of industrial antigens.

Objective/Methodology

This study was performed to evaluate the safety and the efficacy of the subcutaneous injection of one-ml dose of four monovalent BTV1 inactivated vaccines formulated with different payloads and one trivalent BTV1- 4-8 vaccine in sheep.

Seronegative sheep to Bluetongue virus, less than 3 months on Day 0 (D0), were randomly distributed in 6 groups, including a control group. In the vaccinated animals, 1 dose of the different vaccine preparations was administered by subcutaneous route, and the animals were challenged 23 days after vaccination.

Efficacy was demonstrated by challenge with a virulent BTV-1 and monitoring of rectal temperatures, clinical signs and viraemia (by RT-PCR) and serology (SNT tests) was performed, during a period of 14 days after challenge

Results

- Hyperthermia: The control group presented a clear elevation of rectal temperature and less increase was observed in three of the vaccinated groups; statistically significant difference was observed in all vaccinated groups (except one) when compared to the control group.
- Clinical signs: In general, all control animals registered clinical signs (principally congestion and oedema on the head) with frequency and duration of the signs higher than in vaccinated groups. Global clinical scores (GSC) were calculated. The comparisons showed statistically significant decrease of clinical signs in vaccinates when compared to controls.
- Viraemia: All the sheep were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (peak of viraemia 9 days after the challenge). In three of the vaccinated groups, some animals were registered RT-PCR positive; in the two remaining vaccinated groups no animal was ever found viraemic during the full study animals. Controls had significanty higher levels of viraemia when compared to vaccinates.
- Serology: All sheep were BTV-1 sero-negative before vaccination, and the control sheep remained sero-negative until challenge. In the groups with low payload of BTV1 antigens weak or no sero-conversion were observed; and in the other BTV-1 vaccinated groups sero-conversion was observed in most or all the animals. Similar observations occur with BTV 4 and 8 SN tests.

Conclusion

Based on the results of this study, it was concluded that all the tested vaccines had a very good safety and that a dose-effect relation was observed regarding efficacy.

The formulated vaccine with a high antigen payload (BTV1) per dose as well as the trivalent vaccine significantly protected from clinical signs and completely prevent viraemia in all sheep.

This study also supported the absence of interference of BTV8 on the efficacy of BTV1.

Efficacy assessment of vaccines formulated at different payloads of BTV-1 antigen, in presence or not of BTV-8 antigen, administered in 2 injections to sheep

Objective/Methodology:

This study was performed to evaluate the efficacy of the subcutaneous injection of two 1ml -doses of four monovalent BTV1 inactivated vaccines formulated with different payloads and one bivalent BTV1-8 vaccine in sheep.

Sero-negative sheep to Bluetongue virus, approximately 4 months on Day 0 (D0), were randomly distributed in 6 groups, including a control group. In the vaccinated animals, 2 doses of the different vaccine preparations were administered by the subcutaneous route (D0 and D21), and the animals were challenged 23 days after 2nd vaccination.

Efficacy was demonstrated by challenge with a virulent BTV-1 strain and monitoring of rectal temperatures, clinical signs and viraemia, during a period of 14 days after challenge

Results

- Hyperthermia: The control group presented a clear elevation of rectal T and for all the vaccinated groups, the temperature was consistent at the same level and no peak of hyperthermia was registered in any case; controls had increased levels of hyperthermia and statistically significantly higher when compared to all vaccinated groups.
- Clinical signs: all control animals registered clinical signs (principally congestion and oedema on the head) with frequency and duration of the signs significantly higher than in vaccinated groups. The Global clinical scores (GSC) were calculated. The comparisons showed statistically significant decrease of clinical signs in vaccinates when compared to controls.
- Viraemia: All the sheep were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (peak of viraemia 9 days after the challenge). None of the sheep of any of the vaccinated groups was detected positive during the study. Controls had significantly higher levels of viraemia when compared to vaccinates.
- Serology: All sheep were BTV-1 sero-negative before vaccination, and the control sheep remained sero-negative until challenge. A relation between antigen payload/serological response was observed. The booster effect after BTV 1 challenge was clear in all vaccinated animals. Similar observations occur with BTV 8 SN tests, and no booster effect was observed in this case after BTV 1 challenge.

Conclusion

Based on the results of this study, it was concluded that all tested vaccines provided a significant reduction on hyperthermia and clinical signs and a complete prevention of viraemia in all sheep.

A dose-effect relation was observed regarding BTV1 sero-response to the tested vaccines. This study also supports the absence of interference of BTV8 on the efficacy of BTV1.

Assessment of protection against a BTV-8 challenge in sheep

Assessment of (safety) and efficacy by vaccination and challenge in sheep, of vaccines formulated with different BTV-8 antigen payloads

Objective/Methodology: This study was performed to evaluate the safety and the efficacy of the injection of 1ml dose of 6 different BTV vaccines formulated with different payloads of BTV-8 antigen, with or without BTV-2 and BTV-4 antigens in sheep.

Seronegative sheep to Bluetongue virus of 4-5 months on Day 0 (D0), were randomly distributed in 7 groups, including a control group. In the vaccinated animals, 2 doses of vaccine were administered by subcutaneous route, and the animals were challenged 31 days after vaccination.

Efficacy was demonstrated by challenge with a virulent BTV-8 strain and monitoring of rectal temperatures, clinical signs and viraemia, during a period of 14 days after challenge

Results

- Hyperthermia: The control group presented a clear elevation of rectal temperature and for all the vaccinated groups, the temperature no significant elevation was observed.
- Clinical signs: In general, all control animals registered clinical signs (principally congestion and oedema on the head) with frequency and duration of the signs significantly higher than in vaccinated groups. Global clinical scores (GSC) were calculated. The comparisons showed statistically significant decrease of clinical signs in vaccinates when compared to controls.
- Viraemia: All the sheep were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (from D36 to D45). None of the sheep of any of the vaccinated groups was detected positive during the study. Controls had significantly higher levels of viraemia when compared to vaccinates.
- Serology: All sheep were BTV-8 sero-negative before vaccination, and the control sheep remained sero-negative until challenge. A strong serological response was observed in all the groups after challenge. All the animals received BTV8 antigen showed a seroconversion on D31 (whatever the dose). The level of antibodies between groups of vaccinated animals with monovalent batches was similar.

Conclusion

Based on the results of this study, it was concluded that the tested vaccines provided a protection of vaccinated animals with BTV8 associated with a significant prevention of infection.

This study also supported the absence of interference of BTV2 and BTV4 on BTV8 serological response.

Efficacy in sheep of two BTV-8 inactivated vaccines containing low antigen payloads against a BTV-8 challenge

Objective/Methodology

This study was performed to evaluate the efficacy provided by two BTV-8 inactivated vaccines containing low antigen payloads after one subcutaneous administration in sheep .

Seronegative sheep to Bluetongue virus of 5 months on Day 0, were randomly distributed in 3 groups, including a control group. In the vaccinated animals, 1 dose of vaccine was administered by the subcutaneous route and the animals were challenged 22 days after vaccination.

Efficacy was demonstrated by challenge with a virulent BTV-8 and monitoring of rectal temperatures, clinical signs and viraemia, during a period of 15 days after challenge

Results

- Hyperthermia: The control group presented a clear elevation of rectal temperature. In one of the vaccinated groups there was no significant elevation whereas a low increase was observed in the other vaccinated group (this group had significantly lower values than the control group).

- Clinical signs: All control animals registered clinical signs (principally congestion, oedema on the head, erythema and nasal discharge) with frequency and duration of the signs markedly higher than in vaccinated groups. Global clinical score (GSC) was calculated. The comparisons showed statistically significant decrease of clinical signs in vaccinates when compared to controls.
- Viraemia: All the sheep were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (peak of viraemia 10 days after the challenge). None of the sheep from one of the vaccinated groups was detected positive during the study, but there were two positive animals from the vaccinated group with the lowest antigen payload at the first date of monitoring but they remained negative for the rest of the study. Controls had significantly higher levels of viraemia when compared to vaccinates.
- Serology: All sheep were BTV-8 sero-negative before vaccination, and the control sheep remained sero-negative until challenge. No evolution of antibodies was observed in vaccinated groups 14 and 21 days following vaccination.

Conclusion

Based on the results of this study it was concluded that the vaccine batch formulated with the highest antigen payload demonstrated protection against BTV clinical signs, hyperthermia and totally protection against viraemia.

The vaccine batch formulated with the lowest antigen payload demonstrated a significant protection against clinical signs and hyperthermia, and a partial protection against viraemia.

CATTLE

Assessment of protection against a BTV-1 challenge in cattle

Efficacy (and safety) of BTV1 vaccines after 2 injections in conventional calves

Objective/Methodology: This study was performed to evaluate the efficacy (and safety) of the subcutaneous injection of two 1ml -doses of a monovalent BTV1 inactivated vaccine and one trivalent BTV1-4-8 vaccine in calves.

Seronegative calves to Bluetongue virus of 4-5 months on Day 0 (D0), were randomly distributed in 3 groups, including a control group. In the vaccinated animals, 2 doses of vaccine were administered by the subcutaneous route (D0 and D21), and the animals were challenged 23 days after the 2nd vaccination.

Results

- Clinical signs: Global clinical scores (GSC) were calculated. Clinical signs were discrete and were lower in vaccinated groups. The comparisons were statistically significant between vaccinated groups compared with control group which had lower scores.
- Viraemia: All calves were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (from D49 to the end of the monitoring period). None of the calves of any of the vaccinated groups was detected positive during the study. Controls had significantly higher levels of viraemia when compared to vaccinates.
- Serology: All calves were BTV-1 sero-negative before vaccination, and the control calves remained sero-negative until challenge. All vaccinated calves sero-converted after second vaccination, and both vaccinated groups showed similar levels of BTV-1 neutralising antibodies.

Conclusion

It was concluded that a good safety of trivalent vaccine was demonstrated in calves. Moreover, an absence of interference between serotypes (similar levels of neutralising antibodies for both vaccines) was supported from this study.
After challenge all vaccinated animals remained viraemia negative, while the controls presented few clinical signs and viraemia at high titres to the end of the monitoring period. This was in support of the vaccine's efficacy in calves.

Assessment of protection against a BTV-8 challenge in cattle

Efficacy in young calves of an inactivated BTV-8 vaccine against a BTV-8 challenge

Objective/Methodology

This study was performed to evaluate the efficacy of the subcutaneous injection of two 1ml doses of a BTV8 inactivated vaccine containing a low antigen payload in young calves.

Seronegative calves to Bluetongue virus younger or just 1 month of age on Day 0, were randomly distributed in 2 groups, including a control group. In the vaccinated animals, 2 doses of vaccine were administered by the subcutaneous route (D0 and D21), and the animals were challenged 22 days after 2nd vaccination.

Efficacy was demonstrated by challenge with a virulent BTV-8 and monitoring of rectal temperatures, clinical signs and viraemia, during a period of 4 weeks after challenge

Results

- Hyperthermia: During the vaccination phase**,** on D0 three calves in each group showed a slight hyperthermia due to stress; on D21 all the calves were satisfactory general condition. In respect to rectal temperature (Tº), the mean rectal Tº was higher in the control group than in the vaccinated group (no homogeneous groups) and after the challenge, the mean rectal Tº remained higher in the control group than in the vaccinated group. The difference between the both groups was statistically significant.
- Clinical signs: One calf of each of the two groups had respiratory signs throughout the vaccination phase, and were treated (after treatment the control calf stopped clinical signs, but the vaccinated calf persisted clinical signs and was euthanized on D41 for ethical reasons; necropsy and bacteriology demonstrated pasteurellosis and this animal was no taken in account on GCS). After the challenge, clinical signs started on D42 and was discrete in a few vaccinated and controls (most frequently nasal discharge, lacrymation, hypersalivation or cough), remaining constantly higher in controls than in vaccinated, and showing a significant difference. Control calves also showed vesicles, erosions or ulcers on the head, and nasal discharge. One vaccinated calf impaired its body condition and was found dead on D58*. **(generalized haemorrhagic and congestive lesions probably related to BTV-8 challenge; lesions of chronic peritonitis caused for an intercurrent pathology that induced abnormal susceptibility to the challenge. Positive to RT-PCR (non-protected calf)).*
- The rest of vaccinated animals with very limited symptoms
- Viraemia: All the calves were confirmed RT-PCR negative before challenge. After challenge, all control animals were positive (from D 52). From the vaccinated group only one animal was detected positive during the study. Comparisons were highly significant between control and vaccinated animals.

- Serology: All calves were BTV-8 sero-negative before vaccination, and the control calves remained sero-negative until challenge. All vaccinated and control calves had sero-converted to BTV-8 after the challenge. In the vaccinated group, 40% of calves remained sero-negatives 3 weeks after de 2nd vaccination. These results demonstrated that a weak response in predictive of protection, but the absence of response is not predictive of non protection in vaccinated animals.

Conclusion

Based on the results of this study, it was concluded that except one calf (with an intercurrent digestive pathology at a time of challenge), all the vaccinated calves were significantly protected against BTV-8 clinical signs and viraemia, even when vaccinated with vaccines of lower antigen payload.

Influence of Maternally Derived Antibodies (MDAs)

No specific study was performed to investigate the impact on vaccination of pre-existing maternally derived antibodies (MDAs) to vaccine antigens. Not all authors agree on the persistence of these antibodies. The applicant provided bibliographic references, and also performed a safety study with BTV2-4 vaccine showing that MDA decreased at one month of age and disappeared at 2.5 months of age. As a conclusion, the persistence of MDA in calves and lambs can be considered as being 2 to 3 months. Therefore, when the presence of MDA is possible, animal should not be vaccinated before 2.5 months of age. When there are no MDA antibodies derived from vaccination of the ewe or cow, animals can be vaccinated at 1 month of age.

In the absence of specific studies appropriate warnings were included in the relevant sections of the SPC.

Duration of Immunity (DoI)

No specific study was performed to investigate the duration of immunity of the BTVPUR AlSap 1-8 vaccine. One complete study (conducted with inactivated BTV 2 vaccine in sheep of one dose lasting for 1 year) was provided for the authorisation of BTVPUR AlSap 8 vaccine from the same company to support a DoI of 1 year, and also for this authorisation an interim report of a DoI study with BTVPUR AlSap 8 (two doses) was presented with results after 6 months post-vaccination in sheep. Both studies presented good results to support and demonstrate the DoI of 1 year after vaccination (in sheep and for BTV 8 and BTV 2).

Due to the need to provide authorised vaccines against Bluetongue serotypes 1 and 8 as soon as possible and the considerable time required in order to complete the full duration of immunity studies in line with normal requirements the CVMP can exceptionally accept the current limited data with a view for the applicant to provide the remaining information as soon as available.

The applicant has therefore been requested to perform 6 and 12 months DoI studies in sheep.

Field trials

Data on field trials were not provided. In light of the current requirements in 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), field trials may be omitted. The applicant could not reasonably be expected to provide the results from such 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.

BTVPUR AlSap vaccines (2, 4, 2-4, 8) were used in several countries in a very large number of animals, supporting the efficacy for this vaccine under field conditions (results were included in the respective pharmacovigilance report).

Overall conclusion on efficacy

Data of six laboratory studies were provided in order to support the efficacy of the BTVPUR AlSap 1-8 vaccine (three of them with BTV-1 challenge and three with BTV-8 challenge). In these studies vaccines containing low antigen payloads were included. The proposed indications for use in animals of both target species reflected in the SPC were considered as supported by these studies.

The efficacy of the proposed vaccination scheme in animals of the minimum age (1 month) was only investigated in cattle, however it is noted that safety on both target species minimum-age-animals has been supported and the second vaccination fully supports the successful vaccination in this category of animals in both species. Also the efficacy in both species around 2.5 months of age was demonstrated.

The applicant did not provide any studies with the vaccine under application to support the duration of immunity. However due to the need to provide authorised vaccines against Bluetongue serotypes 1 and 8 as soon as possible and the considerable time required in order to complete the full duration of immunity studies in line with normal requirements the CVMP exceptionally extrapolated data were accepted with a view for the applicant to provide the information as soon as available. Field trials were not provided; this was also exceptionally accepted as the applicant could not reasonably be expected to provide the results from such 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.

The efficacy of the proposed vaccination scheme in breeding males, and the impact of the acquired maternal immunity on the efficacy when vaccinating young animals, were not investigated. Specific warnings in the relevant sections of the SPC were included. The efficacy in pregnant animals of both species was also not investigated, but the safety was assessed and demonstrated.

All these circumstances have been reflected in the SPC and the applicant was requested to perform specific studies to investigate the duration of immunity of the product.

Neither DIVA strategy was implemented, nor data were provided in relation to the development of any strategy allowing the differentiation between infected and vaccinated animals.

The efficacy of the vaccine was considered as acceptable within the context of an authorisation under exceptional circumstances, the provisions of the relevant guideline and the inclusion of specific warnings in the relevant sections of the SPC.

5. Benefit risk assessment

Introduction

BTVPUR ALSap 1-8 is an inactivated vaccine conventionally produced, liquid and ready-to-use, and adjuvanted using a combination of aluminium hydroxide and purified saponin. It is indicated to prevent infection, viraemia and clinical signs in sheep and cattle caused by BTV serotypes 1 and 8. In view of the epidemiological situation, the lack of authorised products (in particular bivalent with the combination of serotypes 1 and 8) and the potential for epizootic spread if urgent measures, including

vaccination, are not taken to control the disease at EU level, this application was considered for an authorisation under exceptional circumstances.

Benefit assessment

Direct therapeutic benefits:

Vaccines are a well established and effective method to control the spread of bluetongue virus.

The objective is to induce sufficient immunity to reduce the level of viraemia below a level where transmission could occur and decrease the impact of clinical signs.

Clinical trials demonstrated that the product is capable of inducing an immune response which prevents viraemia and reduces clinical signs in sheep and cattle. The effect is to prevent transmission and minimise the impact of clinical signs.

Additional benefits

BTVPUR AlSap 1-8 is a standard inactivated vaccine and as such fits in with accepted vaccination practice in the field.

Vaccination has been shown to be safe for use during pregnancy in both sheep and cattle, which is valuable during a widespread vaccination programme usually necessary to control the spread of disease.

The vaccine is inactivated by a validated inactivation method therefore there are no risks of spread of live virus.

The vaccine is a bivalent vaccine thus enabling protection against 2 serotypes at the same time while administering one product and following one vaccination schedule.

Risk assessment

Main potential risks:

a) There is a risk of a small local swelling at the injection site (at most 32 cm^2 in cattle and 24 cm^2 in sheep) which becomes residual 35 days later (≤ 1 cm^2) following vaccination. A transient increase in the body temperature, normally not exceeding an average of 1.1°C, may also occur within 24 hours after vaccination.

b) For the user there is a risk of self injection. Appropriate warnings and advice on the SPC have been included to reduce this risk.

c) For the environment there is negligible risk that the vaccine components may cause unexpected effects to the environment.

d) For the consumer there are no components which require an MRL, therefore there are no concerns over failure to observe an MRL. The product contains adjuvants and excipients found in other marketed products for which the safety has been established previously.

Specific potential risks, according to product type and application:

a) Limited data are available on the duration of immunity. As a result an appropriate revaccination programme cannot be recommended at this stage. Due to the need to provide authorised vaccines against Bluetongue serotypes 1 and 8 as soon as possible and the considerable time required in order to complete the full duration of immunity studies in line with normal requirements the CVMP

can exceptionally accept the current limited data with a view for the applicant to provide the remaining information as soon as available.

b) Limited data are available on the stability of product during storage. It is permissible for a preliminary shelf life of 12 months to be granted for this product due to its exceptional nature. Nevertheless there is a risk that the product may not be stable for this period. Due to the need to provide authorised vaccines against Bluetongue serotype 1 and 8 as soon as possible and the considerable time required in order to complete all stability studies in line with normal requirements the CVMP can exceptionally accept the current limited data with a view for the applicant to provide the remaining information as soon as available.

Risk management or mitigation measures

a) Appropriate warnings have been placed in the SPC to warn of the potential risks to the target animal, end user and environment.

b) No special concern is posed by the final product with respect to the environment, in light of the safety of packaging, of the number of injections and of the maximum quantity administered to animals, of the route and of the method of administration, and disposal.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit risk balance for use in sheep and cattle. The product has been shown to be efficacious for the indication of viraemia prevention and reduction of clinical signs.

The formulation and manufacture of BTVPUR AlSap 1-8 are largely well described and specifications are supported. The applicant is able to detect sub-potent batches thereby ensuring that the product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. The withdrawal period is zero days.

Deficiencies include the limited data presented on the vaccine's stability and duration of immunity. However due to the considerable time required to complete the above studies and the need to provide authorised vaccines against Bluetongue serotypes 1 and 8 as soon as possible the CVMP accepted these limited information with a view for the applicant to provide the remaining information as soon as possible. No field data were presented for this application. However the CVMP considered that it cannot reasonably be expected for the applicant to provide the results from such 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.

Conclusion on benefit risk balance

The information provided in the dossier and in response to points raised is sufficient to confirm an overall positive benefit risk balance under exceptional circumstances.

Justification for the exceptional circumstances status of the application:

The reasons which were considered as relevant in order to acknowledge the exceptional circumstances status of this application were the following:

- Bluetongue disease is spread by insect vectors and therefore presents particular challenges in terms of control due to an inability to prevent transmission from infected animals other than

through insect control combined with reducing or preventing viraemia (virus in the blood) in susceptible animals by means of vaccination

- Bluetongue disease is epizootic in nature and has the potential to result in high morbidity and mortality in susceptible populations, particularly of sheep
- Over the last ten years the Bluetongue epidemiological situation in Europe has changed considerably, with the incursion of new serotypes that have been never reported before and with outbreaks in areas which until now were not considered at risk of bluetongue, as is the case for BTV 8 serotype. Also with the outbreaks of BTV1 declared in Spain, Portugal and France the spread of this serotype to other regions and countries in Europe is possible whereas co-infection with both serotypes has already occurred, with not well studied consequences of the epidemiology and pathology of the disease.
- There is still a small number of vaccines against bluetongue in Europe authorised.
- 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).

Conclusion

Based on the data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the overall benefit-risk balance for BTVPUR AlSap 1-8 was considered favourable for authorisation under exceptional circumstances. However, the authorisation of the product will be subject to annual re-assessment in order to recommend whether the authorisation should be continued or not. In addition, data on the stability and duration of immunity of the vaccine should be provided as stated in the specific obligations of the opinion and satisfactory answers must be given to all other concerns, in order for the authorisation to revert to normal status i.e. no longer exceptional and subject to annual review. Based on the data presented, the CVMP concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.