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SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

CVMP assessment report for annual re-assessment for BTVPUR AlSap 1-8

International non-proprietary name: Inactivated vaccine against bluetongue disease for sheep and cattle

Procedure No. EMEA/V/C/002231/S/0002

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

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Authorised presentations

EU Number	Invented name	Strength	Pharmaceutical form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/10/113/001	BTVPUR AlSap 1-8	Bluetongue virus serotype 1 antigen ≥ 1.9 log10 pixels * Bluetongue virus serotype 8 antigen ≥ 2.1 log10 pixels *	Suspension for injection	Sheep and cattle	Subcutaneous	Polypropylene bottle with butyl elastomer closure	100ml	Box of 1 bottle of 100 doses	Zero days
EU/2/10/113/002	BTVPUR AlSap 1-8	Bluetongue virus serotype 1 antigen ≥ 1.9 log10 pixels * Bluetongue virus serotype 8 antigen ≥ 2.1 log10 pixels *	Suspension for injection	Sheep and cattle	Subcutaneous	Polypropylene bottle with butyl elastomer closure	100ml	Box of 10 bottles of 100 doses	Zero days
EU/2/10/113/003	BTVPUR AlSap 1-8	Bluetongue virus serotype 1 antigen ≥ 1.9 log10 pixels * Bluetongue virus serotype 8 antigen ≥ 2.1 log10 pixels *	Suspension for injection	Sheep and cattle	Subcutaneous	Polypropylene bottle with butyl elastomer closure	50ml	Box of 1 bottle of 50 doses	Zero days
EU/2/10/113/004	BTVPUR AlSap 1-8	Bluetongue virus serotype 1 antigen ≥ 1.9 log10 pixels * Bluetongue virus serotype 8 antigen ≥ 2.1 log10 pixels *	Suspension for injection	Sheep and cattle	Subcutaneous	Polypropylene bottle with butyl elastomer closure	50ml	Box of 10 bottles of 50 doses	Zero days

EU/2/10/113/005	BTVPUR AlSap 1-8	Bluetongue virus serotype 1 antigen ≥ 1.9 log10 pixels * Bluetongue virus serotype 8 antigen ≥ 2.1 log10 pixels *	Suspension for injection	Sheep and cattle	Subcutaneous	Type I glass bottle with butyl elastomer closure	10 ml	Box of 1 bottle of 10 doses	Zero days

* Antigen content (VP2 protein) by immuno-assay.

Product information on the annual re-assessment

Invented name:	**BTVPUR AlSap 1-8**
Active substances:	Bluetongue Virus Serotype 1 antigen Bluetongue Virus Serotype 8 antigen
Pharmaceutical form:	Suspension for injection
Strength:	--
Route of administration:	Subcutaneous use
Target species:	Cattle, sheep
Therapeutic indication:	Active immunisation of sheet and cattle to prvent viraemia* and to reduce clinical signs caused by bluetongue virus serotype 1 and 8. *(below the level of detection by the validation RT-PCR method at 3.68 log10 RNA copies/ml, indicating no infectious virus transmission).
Marketing authorisation holder (name and address):	MERIAL 29 avenue Tony Garnier 69003 Lyon France
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1. Background information on the annual re-assessment

1.1. Submission of the application

The Marketing Authorisation Holder (MAH), MERIAL S.A.S submitted to the European Medicines Agency on 16 November 2012 an application for the annual re-assessment for BTVPUR AlSap 1-8 and requested that the marketing authorization (MA) of the vaccine currently under exceptional circumstances converts to a normal MA in case all the specific obligations are considered as fulfilled. This is the second annual re-assesment of this vaccine (i.e re-assessment of the benefit-risk balance of the product) and the CVMP opinions on the previous one were adopted on 9 February 2012. The European Commission granted on 17 December 2010 a marketing authorisation under exceptional circumstances for this veterinary medicinal product.

1.1.1. Scope of the annual reassessment

The annual re-assessment relates to the following specific obligations:

1. The applicant is required to submit as a matter of priority data relating to the following:
   a) Stability of the vaccine: Results from stability studies with the following intervals should be provided: T21 and T27.
   b) Duration of Immunity: Results from 12 month duration of immunity studies should be provided.

   Progress on the above issues should be reported 6 months following the authorisation of the product.

2. For the first and subsequent annual reassessments the marketing authorisation holder should provide annually an updated risk assessment on the continuous use of the vaccine taking into account the continued need for the vaccine, its history of use over the previous twelve months and progress made in addressing the items that require resolution in order for the authorisation to revert to normal status.

3. The applicant is required to submit 6-monthly Periodic Safety Update Reports (PSURs) starting once the marketing authorisation has been approved and, in addition to the legal requirements applicable to reporting of suspected adverse reactions, the applicant is required to specifically monitor and evaluate the following suspected adverse reactions in the PSURs: abortions, spontaneous death, effects on milk production, local reactions, pyrexia, lethargy and hypersensitivity reactions, including severe allergic reactions. The frequency of submissions of PSUR reports will be assessed at the annual reassessment of the product.

1.1.2 Documentation submitted

The marketing authorisation holder submitted the following documentation:

- Administrative data (cover letter)
- Responses to specific obligations (1, 2 and 3) which include Stability study of the BTVPUR AlSap 1-8 100MLPP vaccine and study reports regarding duration of immunity (12 month results) in cattle and sheep, and an updated benefit-risk assessment, which should be taken into account in the benefit-risk balance, pharmacovigilance data.
- Answers to list of questions "other concerns".

- Specific answers to remaining points of concern regarding the BTV1 and BTV8 antigens quantification.

1.2 Steps taken for the assessment of this annual reassessment

- The application for the second annual re-assessment was submitted on 16 November 2012.
- The procedure started on 11 December 2012.
- An opinion was adopted on 7 February 2013.
- European Commission adopted a Commission Decision on 6 May 2013.

2. Scientific discussion

2.1. Assessment

The MAH submitted one document providing the remaining data regarding the specific obligations; another document, as the answers to the remaining point of concern (minor questions) raised by the CVMP during the last annual re-assessment and two other documents, containing specific answers to the remaining point of concern regarding the BTV1 and BTV8 antigens quantification.

Specific Obligations

1st specific obligation:

The applicant is required to submit as a matter of priority data relating to the following:

a) Stability of the vaccine: Results from stability studies with the following intervals should be provided: T21 and T27.

b) Duration of Immunity: Results from 12 month duration of immunity studies should be provided.

Progress on the above issues should be reported 6 months following the authorisation of the product.

In order to address the first specific obligation (action plan for remaining outstanding points) an action plan was submitted by the MAH on 15 June 2011. A number of points still remained outstanding in the corresponding CVMP assessment report.

Data relating to the first specific obligation were further submitted in the context of the current procedure and are presented below:

a) Stability of the vaccine:

Stability of the 100 ml presentation

Study: Stability study of the BTVPUR AlSap 1-8 100MLPP vaccine

A final report was submitted relating to 18-month and 24-month stability of the 100 ml polypropylene bottles of the vaccine. The objective was to evaluate the biological and chemical stability of the vaccine over a 27-month period, on three batches stored protected from light at 5 ± 3 ºC. The parameters monitored during 27 months were the main biological activity (activity challenge of BTV-1 and BTV-8, bacterial and fungal sterility), physico-chemical data (appearance, pH, volume, formaldehyde and aluminium content) and safety. The results of the potency tests in sheep showed a satisfactory activity against BTV8 (90.2 - 100%, limit of acceptance: ≥ 75%) and against BTV-1 (80.0 - 97.3%, value for one batch (97.3%) at T30 instead T27) after 27-months storage. For BTV-1, in few cases at earlier time points satisfactory activity results were obtained not at first testing, however after

retesting stability was confirmed. No major changes in appearance, pH, volume, aluminium content and formaldehyde were reported.

The CVMP concluded that he study conducted on three industrial batches shows a good stability of BTVPUR AlSap 1-8 (100 ml polypropylene vial) after 27 months of storage, under the described conditions (protected from light at 5 ± 3 ºC). The stability of the BTVPUR AlSap 1-8 100 ml polypropylene vial during the investigated 27 months of storage (protected from light at 5 ± 3 ºC) has been confirmed.

The change of the shelf-life of the 100 ml presentation, currently 1 year, to 2 years is supported.

Stability of the 50 ml presentation

Study: Stability study of the BTVPUR AlSap 1-8 50 MLPP vaccine

A study was submitted relating to 12- month and 18- month stability of the 50 ml polypropylene bottle presentation of the vaccine. The objective is to evaluate the biological and chemical stability of the vaccine over a 27-month period, on three batches (50 ml vials stored protected from light at 5 ± 3 ºC). An intermediate report for the first 21month has been provided. The parameters monitored during the first 21-months were the main biological activity (activity challenge of BTV-1 and BTV-8, bacterial and fungal sterility), physic-chemical data (appearance, pH, volume, formaldehyde and aluminium content) and safety. The results of the potency test in sheep showed a satisfactory activity against BTV-1 and BTV-8 after 21-month storage. Only one value slightly lower than expected at T15 (74.2%) was seen for BTV-1 strain. However, this activity was measured again at the next time point and the results (90.1%) were satisfactory. No major changes in appearance, pH, volume, aluminium content and formaldehyde were reported.

The CVMP concluded that the stability of the vaccine BTVPUR AlSap 1-8, 50 ml polypropylene bottle presentation, during the proposed 18-months of storage (protected from light at 5 ± 3 ºC) has been confirmed. The results were within the limits and conform with the specifications, during the studied period (T0 to T21 months). This result can be extrapolated to BTVPUR AlSap 1, as the BTV-1 strain tested is the same in both vaccines and the manufacturing processes for both vaccines are similar.

The change of the shelf-life of the 50 ml presentation, currently 1 year, to 18 months is supported.

Stability of the 10 ml presentation

The study concerning the 12-month and 18-month stability for the 10 ml presentation is currently on-going and results will be available in April and October 2013 and April 2014. Satisfactory results have been obtained after 6 months.

The CVMP concluded that given the fact that the results for the 12 and 18 month stability is still outstanding the shelf-life of the vaccine BTVPUR AlSap 1-8 10 ml prolypropylene bottle remains at 1 year.

Taking into account the fact that the stability studies for the 100 ml and 50 ml presentations, which had been requested from the MAH, have been completed and shown satisfactory stability allowing to extend the shelf-life of these presentations, and the study on the 10 ml presentation is underway and has produced satisfactory results after 6 months, the CVMP agreed that this specific obligation can be considered fulfilled. Based on the stability data available and taking into consideration that the current shelf-life is set at 12 month, no concern arises regarding from the absence of a final stability report for the 10 ml presentation. The CVMP therefore concluded that the absence of a final stability report for the 10 ml presentation should not delay the conversion of the marketing authorisation. Any change to the shelf-life after completion of the study will have to be enacted through a normal regulatory

variation procedure.

b.1) Duration of immunity regarding BTV-1 antigen

Final reports of two efficacy studies to establish duration of immunity of the vaccine in sheep and cattle were provided (study report titled "Duration of immunity of an inactivated BTV1 vaccine after 2 injections 21 days apart in sheep – BTV-1 challenge 12 months after the second administration" and study report titled "Duration of immunity of an inactivated BTV-1 vaccine administered in 2 injections, 3 weeks apart, and to young cattle - Assessment of protection against a BTV-1 challenge 12 months after vaccination").

Study Duration of immunity of a BTV-1 vaccine after 2 injections, 21 days apart, in sheep. BTV-1 challenge 12 months after the second vaccination

The objective was to assess the protection conferred by a BTV-1 inactivated vaccine administered twice 21 days apart to conventional sheep against a BTV-1 antigen. In a preceding experiment thirteen 2-months aged sheep (male and female) were allocated to two groups: the animals in one group (n = 6) were vaccinated according to a vaccination scheme of 2 injections 3 weeks apart with a BTV-1 inactivated vaccine; the second group (n = 7) remained unvaccinated (control group). In the second study, all 13 animals (vaccinated animals and control group) were challenged with a virulent BTV-1 antigen, 12 months after completion of the vaccination.

The virus used in this study came from a vaccine batch containing low content of BTV-1 antigen. The challenge material consisted of red blood cells (RBC) collected from infected sheep. All animals were confirmed qRT-PCR negative before the challenge. The animals were monitored until 14 days after challenge for serology, rectal temperature, clinical signs and viraemia.

Marked elevation of hyperthermia was observed in the control group on D7 with an increase of 2.1 ºC in average compared to D0. Contrary to this, in the vaccinated group, there was no significant elevation with an increase of 0.2 ºC in average after challenge. Maximal hyperthermia in controls was a mean of 41.8 ± 0.4 ºC and in vaccinated a mean of 39.7 ± 0.2. The statistical difference between the groups was highly significant.

After challenge, all the animals in the control group showed clinical signs as congestion of the head (all animals), oedema, erythema and nasal discharge (most animals); nasal erosions, locomotion troubles, erosion of nostrils, apathy, respiratory troubles (polypnea), thinness, apathy and depression were frequently observed (4/7). The vaccinated group only showed congestion of the face in two sheep and nasal discharge and/or erythema in one sheep. The difference between the groups was highly significant.

In the control group, all sheep were positive at all points after challenge from D5 onwards. In contrast, all vaccinated animals remained negative during the study, thus demonstrating prevention of viraemia by the vaccination.

All animals were confirmed sero-negative before vaccination and the control remained sero-negative until the challenge. The first vaccination induced a limited evolution of BTV-1 antibody titres. The second vaccination induced a clear sero-conversion in all vaccinated, and the level of antibodies slightly increased over one year. Both groups were strongly sero-converted after challenge.

The CVMP concluded that the study provided on the efficacy of BTVPUR AlSap 1 with regard to the duration of the immunity in sheep is satisfactory. While the observation period (14 days) after the challenge is shorter compared to the studies in cattle (28 days) presented below, the effects in the vaccinated animals provide a clear evidence of the immunity. The study (challenge results 12 months after completion of vaccination) showed that immunisation with the tested vaccine provided a

significant reduction of hyperthermia, a significant reduction of clinical signs and prevention of viraemia. The data provided support changing the duration of immunity in sheep from currently 6 months to 12 months in respect to the BTV-1 antigen.

Study: Duration of immunity of a BTV-1 vaccine administered in 2 injections, 3 weeks apart, to young cattle – Assessment of protection against a BTV-1 challenge, 12 months after vaccination

The objective of the study was to assess the duration of immunity provided by a BTV-1 inactivated vaccine administered twice 21 days apart to young cattle against a BTV-1 antigen. During the present study, all the cattle were challenged 12 months after completion of the vaccination with a virulent BTV-1 antigen. The efficacy of the vaccination was assessed through clinical and virological (by qRT-PCR) monitoring until 28 days after challenge. In a preceding experiment 18 calves between approximately 2.5 - 3.4 months of age (males bovine (Holstein)) were allocated to two groups: the animals in one group (n= 9) were vaccinated according to a vaccination scheme of 2 injections 3 weeks apart with BTV-1 inactivated vaccine; the second group (n=9) remained unvaccinated (control group). In the second study all 9 vaccinated animals and 8 animals of the control group (one was excluded before challenge) were challenged with a virulent BTV-1 antigen, 12 months after completion of the vaccination. The virus used in this study came from a vaccine batch containing low content of BTV-1 antigen. The challenge material consisted of red blood cells collected from infected sheep. The animals were monitored during 28 days after challenge for serology, rectal temperature, clinical signs and viraemia.

Elevation of temperature between D5 and D16 with peaking on D5 was observed in the control group with maximal of 40.3 ºC, whereas in the vaccinated group, maximal hyperthermia never exceeded 39.4 ºC. The statistical difference between groups was highly significant (vaccinated with mean 39.1 ± 0.2 ºC as compared to the control group with mean 39.8 ± 0.4 ºC). Before the challenge (D0) no clinical sign was recorded in both groups, except occasional lacrimation in one animal of each group and frequent nasal discharge, and due to the unexpected high frequency of the later, this sign was not considered as specific after challenge. After challenge, the global clinical scores in the control group were slightly elevated as usually observed in BTV-1 infections in cattle. The mean of daily clinical scores (DCS) remained low (< 0.4) and individual global clinical scores (GCS) were at most of 3 (4/9 with GCS of 0) except in one animal where it reached 12 but only related to lacrimation (vaccinated group with mean GCS of 2.3 ± 4.1 and control group with mean GCS of 3.8 ± 3.6). All animals were confirmed qRT-PCR negative before the challenge. In the control group, from D5 onwards all animals were positive at all points after challenge. In contrast, all vaccinated animals were negative during the study, thus demonstrating significant reduction of viraemia by the vaccination.

All animals were confirmed sero-negative before vaccination. The control animals remained sero-negative until challenge. A slight seroconversion was observed in several vaccinated animals after first vaccination. Three weeks after second vaccination a clear seroconversion was observed in all vaccinated animals. The level of BTV-1 antibodies slightly decreased over 12 months (until the challenge). Both groups strongly seroconverted after this challenge.

The CVMP concluded that the study provided on the efficacy of BTVPUR AlSap 1, with regards to the duration of the immunity in cattle, is satisfactory. The study (challenge results 12 months after completion of vaccination) showed that immunisation with the tested vaccine provided a significant reduction of hyperthermia and prevention of viraemia. Although reduction of the clinical signs was not as significant compared to the other effects, the prevention of viraemia against an infection by BTV-1 virulent virus was clearly demonstrated by the qRT-PCR results. The data provided support changing the duration of immunity in cattle from currently 6 months to 12 months in respect to the BTV-1 antigen.

b.2) Duration of immunity regarding BTV-8

Final reports of two efficacy studies to establish the duration of immunity of the vaccine in sheep and cattle were provided (study report titled "Duration of immunity of an inactivated BTV-8 vaccine administered to sheep in one to 2 injections"- Protection conferred by the vaccine against virulent BTV-8 challenges performed 6 or 12 months after vaccination" and study report titled "Duration of immunity of BTVPUR AlSap 8, assessment of protection in cattle against a BTV-8 challenge, 12 months after vaccination").

Study: Duration of immunity of a BTV-8, vaccine administered to sheep in one or two injections - Protection conferred by the vaccine against virulent BTV-8 challenges performed 6 or 12 months after vaccination.

The objective of the study was to assess the protection conferred by an inactivated BTV-8 vaccine containing a low antigen payload, after one or two administrations (second administration 28 days after the first) in sheep. Vaccine protection was evaluated by a BTV-8 challenge performed 6 and 12 months after vaccination. The study was conducted with a total of 43 conventional sheep, ca. 6-month old at D0 allocated in 6 groups, with 7 and 8 animals in the two unvaccinated control groups (G0a and G0b), and two groups of 7 animals each vaccinated at D0 (G1a and G1b), and two groups of 7 animals each vaccinated at D0 and D28 (G2a and G2b). After 6 months (D197) the first control group with 7 animals (G0a), and one group of 7 animals vaccinated only once (G1a) and one group with 7 animals vaccinated twice (G2a) were challenged with a virulent BTV-8 antigen. The second control group with 8 animals (G0b), the second group of 7 animals vaccinated only once (G1b) and the second group with 7 animals vaccinated twice (G2b) were challenged after 12 months (D365). The challenge material consisted of red blood cells collected from infected sheep. The animals were monitored until 14 days after challenge for serology, rectal temperature, clinical signs and viraemia.

Results of challenge after 6 months:

Marked elevation of temperature on D7 after the challenge was observed in the control group with an increase of 1.6 ºC in average compared to D197, i.e. before the challenge. In parallel, in the vaccinated groups G1a and G2a, there was no significant elevation with an increase of 0.3 ºC and 0.1 ºC respectively in average compared to D197. Highest hyperthermia was observed in the control group with a mean of 41.4 ± 0.4 ºC; in the once vaccinated group (G1a) the mean was 39.8 ± 0.3 ºC and in the twice vaccinated group (G2) the mean was 39.8 ± 0.3 ºC. The statistical difference between each vaccinated group and the control group was significant. In general, a significantly lower average rectal temperature was observed in both vaccinated groups compared to the control group.

After challenge, all animals in the control group showed clinical signs as congestion and oedema; erythema was frequently registered during 2-3 consecutive days; apathy, petechias, hypersalivation, nasal discharge and crust were occasionally observed. In the once vaccinated group G1a only congestion of the head and erythema was occasionally observed; in the twice vaccinated group G2a only congestion of the eyes was recorded once in one sheep (the mean GCS of the control group was 34.6, of the once vaccinated group G1a 2.9 and of the twice vaccinated group G2a 0.3). The mean daily clinical score in the control group peaked on D204 at a value of 6.1 and remained constantly higher than the vaccinated groups (0.6 and 0.1 respectively). The difference between the vaccinated groups and the control group was significant.

In the control group, all sheep were positive at all points after challenge; conversely, all vaccinated animals (G1a and G2a) remained negative during the study. The viraemia was highly prevented.

Efficacy results 12 months post-vaccination:

A marked elevation on D7 after the BTV-8 challenge, was observed in the control group G0b with an increase of 2.4 ºC in average compared to D365. In parallel, in the vaccinated groups G1b (one vaccine injection) and Gb2 (two vaccine injections), there was no significant elevation with an increase of 0.6º and 0.5 ºC respectively in average compared to D365. Maximal hyperthermia in controls was a mean of 41.7 ± 0.3 ºC; in G1b (once vaccinated) the mean of maximal hyperthermia was 39.9 ± 1.0 ºC (in one sheep the rectal temperature reached 42.0 ºC); in G2b (twice vaccinated) the mean of maximal hyperthermia was 39.8 ± 0.6 ºC. The statistical difference between each vaccinated group with the controls was significant. In general, a significantly lower average rectal temperature was observed in both vaccinated groups compared to the control group.

After challenge, all animals in the control group showed clinical signs as congestion of head and oedema; erythema was frequently registered during 3-5 consecutive days, and nasal discharge was recorded at least once in 7 out of the 8 animals; thinness, apathy, petechias, hypersalivation and locomotion troubles were occasionally observed. Respiratory distress and prostration were observed in one sheep. In the once vaccinated group (G1b), except in one sheep that showed congestive lesions on the head several days, only congestion of the eyes and nasal discharge was sporadically observed. In the twice vaccinated group (G2b) only congestion of the eyes was recorded once in one sheep (the mean global clinical score of the control group was 52.4, of the once vaccinated group G1b 3.6 and of the twice vaccinated group 0.9). The mean daily clinical score of the control group peaked on D 372 at a value of 7.6 and remained constantly higher than the vaccinated groups (0.6 and 0.1 respectively). The difference between the each vaccinated groups and control group was significant.

In the control group, all sheep were positive at all points after challenge; in the once vaccinated group G1b all animals remained negative during the study, except one sheep where viraemia was recorded at the first 4 days at a low level. In the twice vaccinated group G2b all sheep remained negative after challenge. The viraemia was highly prevented.

All animals included in the study were confirmed seronegative to BTV-8 on D0 before vaccination and the control remained seronegative until the challenge either at D 197(G0a, G1a, G2a) or D 365(G0b, G1b, G2b), confirming the susceptibility of animals and the absence of contamination until challenge; a clear seroconversion was seen on week 7 in the four vaccinated groups with higher antibodies titres in the groups with two vaccine injections (G2a and G2B) than in the group with one vaccine injection (G1a and G1b). In G1 the titres remained stable whereas they decreased on week 13 in G2a to remain at a higher level than in G1a and stable until the end of the post-vaccination period. After BTV-8 challenges, a strong serological response was observed in all vaccinated groups. Both regimens tested (one injection or two injections 4 weeks apart) using an inactivated BTV-8 vaccine provided satisfactory results against challenges 6 and 12 months after vaccination.

The CVMP concluded that the study provided on the efficacy of BTVPUR AlSap 8 with regard to the 12 months duration of the immunity in sheep is satisfactory. The study showed that immunisation with the tested vaccine provided a significant reduction of hyperthermia and prevention of viraemia. Although reduction of the clinical signs was not as significant compared to the other effects, the prevention of viraemia against an infection by BTV-8 virulent virus was clearly demonstrated by the qRT-PCR result.

Six and twelve months after vaccination, the two-shot vaccination tested was protective against a BTV-8 challenge as demonstrated by significant reduction of hyperthermia and clinical signs with almost full clinical protection and total prevention of viraemia (as demonstrated by qRT-PCR) in all vaccinated animals.

However, with the one-shot vaccination scheme, one sheep from the vaccinated group showed a moderate form of the disease and a reduced viraemia as compared to the animals in the control group. In summary, after 12 months, the one-shot vaccination programme induced highly significant reduction of specific clinical signs, hyperthermia and viraemia with 85% of the sheep protected. Thus, in order to assure the complete prevention of the viraemia in vaccinated animals after the 12-months BTV-8 challenge, it is necessary to complete the vaccination scheme with two injections 4 weeks apart.

The change of duration of immunity in sheep against BTV-8 antigen, currently 6 months, to 12 months is supported only for the two-shot vaccination scheme. More studies would be necessary to provide the complete prevention of viraemia with the one-shot scheme.

Study: Duration of immunity of a BTVPUR AlSap 8 vaccine, administered in 2 injections, 3 weeks apart, to young cattle - Assessment of protection against a BTV-8 challenge, 12 months after vaccination

The objective of the study was to assess the duration of immunity provided by BTV-8 inactivated vaccine administered twice 3 weeks apart in cattle against BTV-8 antigen. In a preceding experiment 19 calves between approximately 2.1 - 3.4 months of age (males) were allocated to two groups: the animals in group (n= 10) were vaccinated according to a vaccination scheme of 2 injections, 3 weeks apart, with BTV-8 inactivated vaccine; the second group (n=9) remained unvaccinated (control group). In the present study, all animals (vaccinated and controls) were challenged with a virulent BTV-8, 12 months after completion of the vaccination. The efficacy of the vaccination was assessed through serology, monitoring of rectal temperature, clinical signs and viraemia up to 28 days after challenge. The virus used in this study came from an industrial vaccine batch containing low content of BTV-8 antigen. The challenge material consists of red blood cells collected from infected sheep.

Elevation of temperature peaking on D5 was observed in the control group with maximal of 40.3 ºC, whereas in the vaccinated group, maximal hyperthermia never exceeded 39.7 ºC, and no peak of hyperthermia was observed. The statistical difference between groups was highly significant (vaccinated with a mean value of 39.0 ± 0.3 as compared to the control group with a mean value of 39.6 ± 0.5 ºC). After challenge, the most frequently observed clinical signs in the control group were nasal discharge (pre-existing before the challenge), lacrimation and oral or nasal erosions/ulcers. In the vaccinated group clinical signs were nasal discharge and lacrimation (one animal). The mean of the global clinical scores of the vaccinated group was significantly reduced as compared to the control group (ca. 0.5).

All animals were confirmed qRT-PCR negative before the challenge. In the control group, from D5 onwards almost all animals were positive at all points after challenge; in contrast, all vaccinated animals were negative during the study, thus demonstrating significant reduction of viraemia following vaccination. All animals were confirmed seronegative before vaccination. The control animals remained seronegative until challenge. Three weeks after second vaccination, a clear seroconversion was observed in all vaccinated animals. The level of BTV-8 antibodies very slightly decreased over 12 months until the challenge.

The CVMP concluded that the study provided on the efficacy of BTVPUR AlSap 8, with regards to the duration of the 12 months duration of immunity in cattle, is satisfactory and applicable to BTVPUR AlSap 1-8. The study (challenge results 12 months after completion of vaccination) showed that immunisation with the tested vaccine provided a significant reduction of hyperthermia and prevention of viraemia. Although reduction of the clinical signs was not as significant compared to the other effects, the prevention of viraemia against an infection by BTV-8 virulent virus was clearly demonstrated by the RT-PCR results.

Overall conclusions on efficacy of BTVPUR AlSap 1-8:

Based on the results of the efficacy studies in sheep and cattle for BTVPUR AlSap 1 and BTVPUR AlSap 8 the change of duration of immunity for BTVPUR Alsap 1-8 in both sheep and cattle, currently 6 months, to 12 months is supported, based on a scheme of two vaccinations for both sheep and cattle.

A one-shot vaccination scheme for sheep cannot be supported on the basis of the data provided.

2nd specific obligation

For the first and subsequent annual reassessments the marketing authorisation holder should provide annually an updated risk assessment on the continuous use of the vaccine taking into account the continued need for the vaccine, its history of use over the previous twelve months and progress made in addressing the items that require resolution in order for the authorisation to revert to normal status.

In the context of the second specific obligation, an updated risk assessment was submitted by the MAH that addressed the remaining need for the product in the EU. It also included information from the use of the vaccine over the previous twelve months. According to the information available on the EU Surveillance Network for Bluetongue web site (http://www.eubtnet.izs.it/btnet/), there were 8 new outbreaks of BTV -1 (Italy, Spain and Portugal) and 1 new outbreak of BTV -8 (in Italy), between May 2011 and February 2012 in European countries, and 39 outbreaks of BTV-1 were reported in Tunisia during the same period. These outbreaks illustrated that this serotype remains a potential threat for European countries.

In 2012 the bivalent BTVPUR AlSap 1-8 was sold in France, Spain and Italy. The risk assessment of the use of the vaccine was presented in the two PSURs report, and no updated of the SPC and literature was necessary.

The CVMP concluded that the data submitted above was satisfactory and the updated benefit-risk balance justified the maintenance of the product in the EU market.

3rd specific obligation

The applicant is required to submit 6-monthly Periodic Safety Update Reports (PSURs) starting once the marketing authorisation has been approved and, in addition to the legal requirements applicable to reporting of suspected adverse reactions, the applicant is required to specifically monitor and evaluate the following suspected adverse reactions in the PSURs: abortions, spontaneous death, effects on milk production, local reactions, pyrexia, lethargy and hypersensitivity reactions, including severe allergic reactions. The frequency of submissions of PSUR reports will be assessed at the annual reassessment of the product.

In order to address the third specific obligation two PSURs were submitted in the context of this procedure including a risk assessment of the use of the vaccine covering the periods 01 July 2011 to 31 December 2011 and 01 January 2012 to 30 June 2012.

Taking in account both periods, eighteen adverse events occurred worldwide, and no update of the SPC and product literature was necessary.

Sixteen adverse events were serious and two non-serious, all occurred after recommended use in target species (seventeen in bovine and one in ovine). No adverse events in humans or suspected lack of expected efficacy events in animals were reported.

An incidence of 0.00083% was calculated, equivalent to 1 animal per 120,736 treated.

The clinical signs shown were: systemic disorders (anorexia, lethargy, pyrexia and death),

reproductive system disorders (abortion and foetal reabsorption), application site disorders (oedema and pain), mammary gland disorders (milk production decrease), neurological disorders (ataxia, paralysis and blindness) and musculoskeletal disorders (lameness), respiratory tract disorders and immune system disorders (anaphylaxis).

The CVMP concluded that both PSURs showed that the use of the product was consistent with the cumulative experience to date and with the approved label text. No update of the SPC and product literature was deemed necessary as a result of safety concerns from those reports. There is no need to await the assessment of the forthcoming PSUR before deciding the conversion of the current MA to normal status. Considering the pharmacovigilance data submitted for BTVPUR AlSap 1-8 for the years 2011 and 2012 it is recommended that the submission of future PSURs should follow the standard timetable, following the conversion of the MA.

Other concerns

The answers to the minor questions that require resolution in order for the authorisation to convert to normal status were submitted with this annual re-assessment.

These have been satisfactorily answered.

A number of points for concern relating to the quality (including issues on the quantification of antigen in the final product and stability of the active substance) part of the dossier remained to be resolved following the last annual reassessment. These have been satisfactorily addressed.

2.2. Summary and Conclusions

The MAH submitted on 16 November 2012 an application for the annual re-assessment of BTVPUR AlSap 1- 8 vaccine. This is the second re-assessment since the authorisation of the vaccine on 17 December 2010 and the MAH requested the CVMP to consider the conversion of the authorisation which is currently under exceptional circumstances to a normal status.

In this second annual re-assessment the evidence of compliance against the specific obligations described in the beginning of the report was investigated. During this procedure points for clarification/amendments were addressed by the MAH; they were justified and substantiated satisfactorily. Some points for concern relating to quality issues which remained outstanding following the last annual reassessment were also addressed.

In the context of the second annual re-assessment for BTVPUR AlSap 1-8 the main issues addressed were the following: the stability for the 100 ml, 50ml and 10ml polypropylene bottles was established to be 24, 18 and 12 months respectively. As a result the shelf life in the SPC was updated accordingly. The duration of immunity for sheep and cattle was shown to be 12 months. Also the system for the quantification of antigen in the final product was shown to be suitable; therefore the updating of the antigen content in the SPC (section 2) in line with the VP2 immuno- assay method was acceptable.

The information provided also confirmed the need to maintain the MA in the European Union.

The risk assessment of the use of the vaccine was presented in two PSURs covering the periods 01 July 2011 to 31 December 2011 and 01 January to 30 June 2012. It supported the safe use of the product in the field and did not indicate a need to update the SPC on safety grounds.

As a result of the above the CVMP considered that all the specific obligations were fulfilled and there are no remaining grounds to maintain the marketing authorisation of BTVPUR AlSap 1-8 under exceptional circumstances. Considering the pharmacovigilance data submitted for BTVPUR AlSap 1-8 for the years 2011 and 2012 it is recommended that the submission of future PSUR should follow the standard timetable, following the conversion of the MA.

3. Benefit-risk assessment

Introduction

BTVPUR AlSap 1-8 is an inactivated vaccine against bluetongue serotype 1 and 8. The vaccine is formulated to contain aluminium hydroxide and saponin as an adjuvant system. The product has been authorised in 2010 under exceptional circumstances due to the epidemiological situation at the time. This is the second annual re-assessment and the MAH has requested the conversion of the authorisation to a normal one on the basis of having fulfilled all specific obligations.

3.1. Benefit assessment

BTVPUR AlSap 1-8 is a vaccine containing inactivated serotype 1 and 8 bluetongue virus antigens combined with an adjuvant intended to induce an immune response in sheep and cattle, with the aim of preventing infection and of reducing clinical signs caused by the bluetongue virus serotypes 1 and 8.

Direct therapeutic benefit

The benefit of BTVPUR AlSap 1-8 is to induce sufficient immunity to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotypes 1 and 8.

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

Clinical trials demonstrated that the product is capable of inducing an immune response which prevents transmission of the virus in both sheep and cattle and reduces clinical signs caused by bluetongue virus serotype 1 and 8.

Additional benefits

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

The change of the duration of immunity from 6 to 12 months has been demonstrated for both cattle and sheep.

Vaccination has also 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.

3.2. Risk assessment

An updated risk assessment was submitted by the MAH that addressed the remaining need for the product in the EU. The risk assessment of the use of the vaccine was based in the two PSURs reports (observation periods Jul-Dec 2011 and Jan-Jun 2012). Altogether, the data submitted confirmed that the updated benefit-risk balance justified the maintenance of the product in the EU market.

Main potential risks:

Quality:

Stability of the vaccine has been demonstrated.

For the target animals:

For sheep and cattle vaccination may be followed by 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). A transient increase in body temperature, normally not exceeding an average of 1.1 °C, may occur within 24 hours

after vaccination. Pharmacovigilance data have confirmed the safety of the product in accordance with the SPC.

For the user:

For the user there is a low risk of self-injection. Appropriate warnings and advice on the SPC are included to minimise the risk.

For the environment:

For the environment there is a very low risk that the vaccine components may cause unexpected effects to the environment. However the vaccine is inactivated by a validated inactivation method and therefore is no risk of the spread of live virus. The adjuvants appear to be pharmacologically inert substances. 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 of the method of administration, and disposal.

For the consumer:

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 components found in other marketed products; therefore the risk is no greater than already exists.

Specific potential risks, according to product type and application

Following the second annual re-assessment, all specific obligations have been fulfilled and no further specific risks have been identified from the use of the product.

Risk management or mitigation measures

Appropriate warnings have been placed in the SPC to inform on the potential risks to the target animals, the user and the environment and provide advice for reducing these risks.

3.3. Evaluation of the benefit-risk balance

BTVPUR AlSap 1-8 has been shown to have a positive benefit-risk balance for use in both sheep and cattle. The product has been shown to be efficacious for the indication of preventing viraemia and of reducing clinical signs caused by the bluetongue virus serotype 1.

The formulation and manufacture of BTVPUR Alsap 1-8 are well described and specifications are supported. The MAH has a suitable system for the antigens quantification in the finished product and for the detection of sub-potent batches thereby ensuring that product of consistent quality will be produced.

It is well tolerated by the target animals and presents a very low risk for users, the environment and the environment. Appropriate warnings have been included in the SPC.

Conclusion on benefit-risk balance

The information provided in the dossier and in response to the specific obligations and other points raised by the CVMP was adequate to confirm an overall positive benefit risk balance.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the overall benefit risk balance was favourable. Moreover since all the specific obligations have been fulfilled, there are no remaining grounds to maintain the marketing authorisation of BTVPUR AlSap 1-8 under exceptional circumstances.

4. Overall conclusions of the evaluation and recommendations

The CVMP reviewed the evidence of compliance with the specific obligations submitted by the MAH and re-assessed the benefit risk balance of this veterinary medicinal product.

The CVMP considered that this application, accompanied by the submitted documentation, demonstrated that the benefit risk profile remains favourable for the product.

Apart from one subsection of the first specific obligation (namely the stability studies for the 10 ml presentation) all specific obligations haven been fulfilled. Taking into account the fact that the stability studies for the 100 ml and 50 ml presentations, which had been requested from the MAH, have been completed and shown satisfactory stability allowing to extend the shelf life for these presentations, and the study on the 10 ml presentation is underway and the results obtained so far have been satisfactory, the CVMP agreed that this specific obligation can be considered fulfilled. Based on the stability data available and taking into consideration that the current shelf-life is set at 12 months, no concern arises from the absence of a final stability report for the 10 ml presentation. Any change to the shelf-life after completion of the study will have to be enacted through a variation procedure.

The CVMP considers that there are no remaining grounds to maintain the marketing authorisation of BTVPUR AlSap 1- 8 under exceptional circumstances.

The CVMP recommends to re-set the periodic safety update report cycle for BTVPUR AlSap 1-8 vaccine according to the standard rules, following the conversion of the MA under exceptional circumstances to a normal one.

4.1. Changes to the community marketing authorisation

Changes are required in the Community marketing authorisation as a consequence of the CVMP proposal to convert the current MA to a normal status. The SPC also needs to be updated in accordance with the latest information provided by the MAH on antigen quantity (section 2), duration of immunity (section 4.2), vaccination schedule (section 4.9) and shelf life (section: 6.3).