



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

CVMP assessment report for annual re-assessment for BTVPUR AISap 1

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

Procedure No. EMEA/V/C/002230/S/0002

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



Authorised presentations

EU Number	Invented name	Strength	Pharmaceutical Form	Target Species	Route of Administration	Packaging	Content	Package size	Withdrawal period
EU/2/10/112/001	BTVPUR AISap 1	Bluetongue virus serotype 1 antigen $\geq 1.9 \log_{10}$ pixels*8.1 CCID50*	Suspension for injection	Cattle, Sheep	Subcutaneous use	Polypropylene bottle	100 ml	1 bottle of 100 doses	N/A (Cattle), N/A (Sheep)
EU/2/10/112/002	BTVPUR AISap 1	Bluetongue virus serotype 1 antigen $\geq 1.9 \log_{10}$ pixels*	Suspension for injection	Cattle, Sheep	Subcutaneous use	Polypropylene bottle	100 ml	10 bottles of 100 doses	N/A (Cattle), N/A (Sheep)
EU/2/10/112/003	BTVPUR AISap 1	Bluetongue virus serotype 1 antigen $\geq 1.9 \log_{10}$ pixels*	Suspension for injection	Cattle, Sheep	Subcutaneous use	Polypropylene bottle	50 ml	1 bottle of 50 doses	N/A (Cattle), N/A (Sheep)
EU/2/10/112/004	BTVPUR AISap 1	Bluetongue virus serotype 1 antigen $\geq 1.9 \log_{10}$ pixels*	Suspension for injection	Cattle, Sheep	Subcutaneous use	Polypropylene bottle	50 ml	10 bottles of 50 doses	N/A (Cattle), N/A (Sheep)
EU/2/10/112/005	BTVPUR AISap 1	Bluetongue virus serotype 1 antigen $\geq 1.9 \log_{10}$ pixels*	Suspension for injection	Cattle, Sheep	Subcutaneous use	Polypropylene bottle	10 ml	1 bottle of 10 doses	N/A (Cattle), N/A (Sheep)

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

Product information on the annual re-assessment

Invented name:	BTVPUR AISap 1
Active substances:	Bluetongue virus serotype 1 antigen
Pharmaceutical form:	Suspension for injection
Strength:	--
Route of administration:	Subcutaneous use
Target species:	Cattle, sheep
Therapeutic indication:	Active immunisation of sheep and cattle to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotype 1.
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 AISap 1 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-assessment 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 14 October 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 a stability study on the BTVPUR AISap 1-8 100 MLPP vaccine, 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 antigen quantification.

Specific Obligations

1st specific obligation

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.

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.

a) Stability of the vaccine:

Stability of the 100 ml presentation

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

A final report was submitted relating to 18-months and 24-months 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 °C.

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 BTV-8 (90.2 - 100%, limit of acceptance: $\geq 75\%$) 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 the study conducted on three industrial batches shows a good stability of BTVPUR AISap 1-8 (100 ml polypropylene vial) after 27 months of storage, under the described conditions. The stability of the BTVPUR AISap 1-8 100 ml polypropylene vial during the investigated 27-months of storage (protected from light at 5 ± 3 °C) has been confirmed. This result can be extrapolated to BTVPUR AISap 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 100 ml presentation, currently 1 year, to 2 years is supported.

Stability of the 50 ml presentation

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

A study relating to 12-month and 18-month stability testing for the 50 ml polypropylene bottle presentation was submitted. 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 °C). An intermediate report for the first 21-month has been provided. The parameters monitored during the first 21-month were the main biological activity (activity challenge of BTV1 and BTV-8, bacterial and fungal sterility), physico-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 activity against challenge remained satisfactory until the end of the reporting period.

The CVMP concluded that the stability of the vaccine BTVPUR AISap 1-8, 50 ml polypropylene bottle presentation, during the proposed 18-month of storage (protected from light at 5 ± 3 °C) 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 AISap 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 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 ongoing and results will be available in April, October 2013 and April 2014. Satisfactory results have been shown after 6 months.

The CVMP concluded that given the fact that the results for the 12 and 18 months stability is still outstanding the shelf-life of the vaccine BTVPUR AISap 1-8 10 ml polypropylene 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) Duration of immunity

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-1 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 13 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 an industrial 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 RT-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 °C in average compared to D0. Contrary to this, in the vaccinated group, there was no significant elevation with an increase of 0.2 °C in average after challenge. Maximal hyperthermia in controls was a mean of 41.8 ± 0.4 °C 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 AISap 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) 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 an industrial 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 °C, whereas in the vaccinated group, maximal hyperthermia never exceeded 39.4 °C. The statistical difference between groups was highly significant (vaccinated with mean 39.1 ± 0.2 °C as compared to the control group with mean 39.8 ± 0.4 °C). 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 (GCS) in the control group showed a lower reduction in comparison with what is 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 AISap 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.

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 point 2 of the list of specific obligations (requirement for an updated risk assessment), 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, between May 2011 and February 2012 in European countries (Italy, Spain and Portugal) 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 monovalent BTVPUR AISap 1 was not sold in the European Union and anywhere in the world. The bivalent BTVPUR AISap 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 point 3 of 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.

In 2012 the monovalent BTVPUR AISap 1 was not sold in the European Union and anywhere in the world. The bivalent BTVPUR AISap 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.

In the period covered from 01 July 2011 to 31 December 2011 three non-serious adverse events were reported, all occurred after recommended use in target species (two 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 0.13047% was calculated, equivalent to 1 animal per 766 treated.

The clinical signs recorded were: Systemic disorders (lethargy and anorexia), digestive tract disorders (abdominal pain and bloat), mammary gland disorders (mastitis) and skin and appendages disorders (bloody crust).

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 AISap 1 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. They 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 AISap 1 vaccine. This is the second re-assessment since the authorisation of the vaccine in 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 AISap 1 the main issues addressed were the following: the stability for the 100 ml, 50 ml and 10 ml 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 AISap 1 under exceptional circumstances. Considering the pharmacovigilance data submitted for BTVPUR AISap 1 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 AISap 1 is an inactivated vaccine against bluetongue serotype 1. 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

Introduction

BTVPUR AISap 1 is a vaccine containing inactivated serotype 1 bluetongue virus antigen 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 serotype 1.

Direct therapeutic benefit

The benefit of BTVPUR AISap 1 is to induce sufficient immunity to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotype 1.

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.

Additional benefits

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

A duration of immunity of 12 months has been satisfactorily demonstrated for both sheep and cattle.

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 cm² in cattle and 24 cm² in sheep) which becomes residual 35 days later (≤ 1 cm²). 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 AISap 1 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 AISap 1 are well described and specifications are supported. The MAH has a suitable system for the antigen 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 AISap 1 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 have 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 of 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. The CVMP therefore concluded that the absence of a final stability study 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 variation procedure.

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

Therefore, the CVMP recommends to re-set the periodic safety update report cycle for BTVPUR AISap 1 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).