EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for the annual re-assessment of BTVPUR AlSap 2-4 (EMEA/V/C/000139/S/0004)

International non-proprietary name: inactivated adjuvanted vaccines against bluetongue virus serotype 2 and 4 infections

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/2/10/108/001	BTVPUR AlSap 2-4	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50*	Suspension for injection	Sheep	Subcutaneous use	Box of polypropylene bottle with butyl elastomer closure.	100 ml	1 bottles	Zero days
EU/2/10/108/002	BTVPUR AlSap 2-4	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50*	Suspension for injection	Sheep	Subcutaneous use	Box of polypropylene bottles with butyl elastomer closure.	100 ml	10 bottles	Zero days
EU/2/10/108/003	BTVPUR AlSap 2-4	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50*	Suspension for injection	Sheep	Subcutaneous use	Box of polypropylene bottle with butyl elastomer closure.	50 ml	1 bottles	Zero days
EU/2/10/108/004	BTVPUR AlSap 2-4	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50*	Suspension for injection	Sheep	Subcutaneous use	Box of polypropylene bottles with butyl elastomer closure.	50 ml	10 bottles	Zero days
EU/2/10/108/005	BTVPUR AlSap 2-4	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50*	Suspension for injection	Sheep	Subcutaneous use	Box of type I glass bottle with butyl elastomer closure.	10 ml	1 bottle	Zero days

(*) equivalent to titre prior to inactivation (log_{10})

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Product information on the annual re-assessment

Invented name:	**BTVPUR AlSap 2-4**
Active substances:	Inactivated adjuvanted vaccine against bluetongue virus serotype 2 and 4 infections
Pharmaceutical form:	Suspension for injection
Strength:	BTV2: 6.8 - 9.5 CCID50* BTV4: 7.1 - 8.5 CCID50* (*) equivalent to titre prior to inactivation (log_{10})
Route of administration:	Subcutaneous use
Target species:	Sheep
Therapeutic indication:	Active immunisation of sheep to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotypes 2 and 4.
Marketing authorisation holder (name and address):	MERIAL S.A.S. 29 avenue Tony Garnier 69007 Lyon France
MAH contact point:	Dr Benjamin Thenoz
Rapporteur:	Maria Tollis

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1. Background information on the annual re-assessment

1.1. Submission of the application

The Marketing Authorisation Holder (MAH), MERIAL submitted in accordance with Article 39(7) of Commission Regulation (EC) No. 726/2004 on 9 December 2013 an application for the third annual re-assessment for BTVPUR AlSap 2-4 to the European Medicines Agency (the Agency) and requested that the marketing authorisation (MA) of the vaccine currently under exceptional circumstances converts to a normal status in case all the specific obligations are considered as fulfilled.

The product contains inactivated bluetongue virus (BTV), serotype 2 (BTV-2) and serotype 4 (BTV-4).

This is the third annual re-assesment for this product BTVPUR AlSap 2-4 (i.e re-assessment of the benefit-risk balance). A marketing authorisation under exceptional circumstances was granted on 5 November 2010 by the European Commission for this veterinary medicinal product.

The CVMP adopted an opinion and CVMP assessment report on 13 February 2014.

On 11 April 2014, the European Commission adopted a Commission Decision for this application.

1.1.1. Scope of the annual reassessment

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

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

a) Stability of the vaccine: The final report concerning the stability results obtained from 3 batches of each presentation should be provided.

b) Duration of Immunity (DoI): Results from 12 month duration of immunity studies should be provided. Additionally, a justification for the interruption of the 6 month DoI study for BTV -4 serotype.

2. The applicant is required to submit data as requested in post-authorisation commitments and to submit in 6 months following the authorisation of the product, an action plan together with timelines for all points that require resolution in order for the authorisation to revert to normal status. The above information will be evaluated and approved by the CVMP and will form part of the subsequent annual reassessment.

3. For the first and subsequent annual reassessments the MAH 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.

4. The applicant is required to submit 6-monthly Periodic Update Safety Reports (PSURs) starting once the MA 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.

With reference to the 2nd specific obligation above, the points that required resolution in order for the authorisation to convert to normal status were listed in the CVMP assessment report of the original application for granting a MA for BTVPUR AlSap 2-4 under “other concerns” and were the following

three as summarised below:

1) Suitable system to quantify the active substance

2) Compliance of hydrochloric acid 35% with Ph. Eur.

3) Duration of local reactions following the administration of an overdose.

1.1.2 Documentation submitted

The MAH submitted the following documentation:

- BTVPUR AlSap 2-4 Annual Re-assessment 2013: Answers to the Letter of Specific obligations.
- BTVPUR AlSap 2-4 Annual Re-assessment 2013: Answers to other concerns.
- Revised Product Information.

1.2 Steps taken for the assessment of this annual reassessment

- The application for the BTVPUR AlSap 2-4 annual re-assessment was submitted on 9 December 2013.
- The procedure started on 17 December 2013.
- An opinion was adopted on 13 February 2014 by the CVMP.

2. Scientific discussion

2.1. Assessment

Specific Obligations

1st Specific obligation

Following the second annual re-assessment the following issues remained to be addressed:

a) *Stability of the vaccine: "The results are still awaited concerning the 12,18,24 months respectively stability for all presentation of BTVPUR AlSap 2-4 vaccine*".

For the third annual re-assessment three reports were provided with stability data regarding the 100 ml, the 50 ml and the 10 ml presentations respectively to address the outstanding issue. For these three studies, a common protocol was used in order to support the authorized 12 months stability of the above presentations of the BTVPUR Alsap 2-4 vaccine. The main physico-chemical (appearance, pH, volume, formaldehyde and aluminium content) and biological (bacterial and fungal sterility, biological activity measured by challenge and safety) parameters of the vaccine were monitored regularly during the 21 first months of the targeted 27 months of the stability studies. Three batches of each presentation of the vaccine were used after appropriate storage. The data obtained after 21 months storage showed that the physico-chemical characteristics of the vaccine remained in compliance with the relevant approved specifications. The sterility and the safety of the vaccine were not impaired during the storage period and the biological activity remained satisfactory following challenge in the target animal species (sheep).

The CVMP concluded that the data provided by the applicant were suitable to support the proposed 18 months shelf life for all presentations of the product.

This issue was considered resolved.

b) "*Duration of immunity (results from 6 and 12 months duration of immunity studies should be provided). Although the proposal to refer directly to the 12 months DoI is acceptable, at present stage DoI for BTV-4 has to be considered as missing. The MAH should detail the reason for the interruption of the 6 months DoI study for BTV-4.*"

For the third annual re-assessment data on the 12-month DoI were made available through the presentation of reports from studies investigating DoI against BTV-2 challenge and DoI against BTV-4 challenge.

One study was provided to investigate the duration of immunity of an inactivated BTV-2 vaccine after a single injection to lambs and to assess the protection against a BTV-2 challenge, 12 months after vaccination.

In this study, 7 vaccinated and 8 control animals (from a previous study) were challenged with a virulent BTV-2 inoculum, 12 months after vaccination. In the previous study, a group of sheep had received one injection of a BTV-2 inactivated vaccine formulated with a low antigen payload . Another group was left unvaccinated and served as control group.

The BTV-2 challenge virus consisted of red blood cells collected from an infected sheep. Each animal was challenged with 3 ml of the BTV-2 virus, by intradermal route. The efficacy of the vaccination was assessed through clinical, virological (qRT-PCR) and serological monitoring up to 14 days post-challenge. On D14, all animals were terminated.

Results showed that all animals were confirmed to be sero-negative before vaccination and the controls remained sero-negative until challenge. Three weeks after vaccination a sero-conversion was observed in several vaccinated animals. At the next time point (approx. 5-6 weeks later), a clear sero-conversion was observed in all vaccinated animals. Thereafter, the average BTV-2 antibody titre in the vaccinated group slightly increased until challenge 12 months after vaccination. Both vaccinated and control animals strongly sero-responded to the BTV-2 challenge.

All the animals were confirmed negative for BTV viral RNA before challenge. In the control group, all animals were detected positive at all selected time points after challenge at high titres. Conversely, in none of the vaccinated animals, viraemia was ever detected.

Statistical analysis performed on the Area under the curve (AUC) parameter concluded to a significant reduction of viraemia in the vaccinated group as compared to the control group ($p=0.0005$).

All vaccinated animals were fully protected from clinical signs, hyperthermia and viraemia after the challenge.

In conclusion, this study demonstrated that the batch used, formulated with a low antigen payload, provided full protection against a virulent BTV-2 challenge in all sheep, 12 months after vaccination. A 12 month DoI against BTV-2 was supported.

Another study was provided to investigate the duration of immunity of an inactivated BTV-4 vaccine, after a single injection to lambs and to assess protection against a BTV-4 challenge, 12 months after vaccination.

In the study, 8 vaccinated and 8 control animals from a previous study were challenged with a virulent BTV-4 inoculum, 12 months after vaccination. In the previous study, a group of sheep had received one injection of a BTV-4 inactivated vaccine, formulated with a low antigen payload. Another group was left unvaccinated and served as control group.

The BTV-4 challenge virus consisted of red blood cells collected from an infected sheep. Each animal was challenged with 3 ml of the BTV-4 virus, by intradermal route. The efficacy of vaccination was assessed through clinical, virological (qRT-PCR) and serological monitoring up to 14 days post challenge. On D14, all animals were terminated.

Results showed that all controls were sero-negative before challenge. All vaccinated animals were sero-positive before challenge, thus confirming the vaccine uptake. All vaccinated animals serologically responded to the challenge. In the control group, 5 animals serologically responded to the challenge while 3 animals did not serologically respond to the challenge.

All animals were confirmed negative for BTV viral RNA before challenge. In the control group, 6 of the 8 animals were detected positive on at least 2 separate time points after challenge, at rather high titres. Two of the controls did not develop any viraemia. Conversely, viraemia was not detected in any of the vaccinated animals. Statistical analysis performed on the AUC parameter showed a highly significant reduction of viraemia in the vaccinated group when compared to the control group ($p=0.005$).

All vaccinated animals were fully protected against significant clinical signs, including hyperthermia, after challenge.

The BTV-4 challenge resulted in typical clinical signs and strong viraemia in 6 of the 8 control animals. In these animals the challenge was considered moderate to severe. The challenge was thus validated. One animal was euthanized on ethical grounds due to a deterioration of its general condition. None of the vaccinated animals presented specific clinical signs or viraemia. All vaccinated animals serologically responded to the challenge, which confirmed the challenge.

In conclusion, this study demonstrated that the batch used, formulated with a low antigen payload, provided full protection against a virulent BTV-4 challenge in all sheep, 12 months after vaccination. A 12 month DoI against BTV-4 is supported.

On the basis of the above studies the recommendation on the duration of immunity for this vaccine is considered resolved. A 12 month DoI against BTV-2 and BTV-4 was adequately justified.

Conclusion on 1st specific obligation

a) Stability: The data provided by the MAH were suitable to confirm 18 months shelf life for the three presentations of the BTVPUR AlSap 2-4 vaccine. This recommendation on stability is considered resolved.

b) DoI: The results obtained from the two presented duration of immunity studies with the monovalent vaccines BTV2 and BTV4 respectively, were suitable to confirm a 12 months duration of immunity of the BTVPUR AlSap 2-4 vaccine.

The 1st specific obligation is considered fulfilled.

2nd Specific obligation

The requested action plan was submitted on 03 May 2011 and the answers to the “other concerns” remaining since the second annual reassessment that require resolution in order for the authorisation to revert to normal status were submitted together for this third annual reassessment.

A note concerning identification of a change in one supplier of adult bovine serum for an update of the part II.C.3 with the name of the supplier was provided and was considered acceptable.

Following the second annual re-assessment the following issues still remained to be addressed in order for the authorisation given under “exceptional circumstances” to convert to normal status.

1. *The marketing authorisation holder is requested to provide a suitable system for quantifying active ingredient at blending (q. 22 of initial "other concerns" in List of Question (LoQ).*

The MAH was requested to comment on a number of points in order to support the validity of the measurement method of the Sero- Neutralising (SN) titre following the initial authorisation of the product. Following the submission of data in the first annual re-assessment it was concluded that the measurement of the SN titre was not relevant any more as it was replaced by the determination of the infectious titre prior to inactivation. A link between the infectious titre prior to inactivation and protection was established. A link was also established with the VP7 ELISA content and consistency of production. Thresholds at blending were thus defined in order to ensure the efficacy from batch to batch. The above were accepted under the condition that a suitable system for quantifying the active ingredient at blending should be provided for the authorisation to revert to normal status.

In this annual re-assessment the MAH argued that although a suitable active ingredient quantification system at blending could allow a better control of the process consistency and vaccine efficacy in the absence of appropriate monitoring and quality control tools, this is currently not the case. The consistency of the BTVPUR AlSap 2-4 vaccine process has already been fully demonstrated as mentioned in the answers to the major list of questions. This active ingredient process can thus be considered as a well-established process.

In addition, quality control results using the analytical tools developed for BTVPUR AlSap 8 vaccine have confirmed the consistency from batch to batch. These control tools were developed with the aim to characterize as much as possible the active ingredient and to prove consistency of the antigen production process.

They are listed below:

- Infectious titre before inactivation,

- HPLC,

- RT QPCR,

- VP7 quantification by ELISA,

- Dot blot (VP2, VP5, VP7).

For release purposes, some of these tests (infectious titre before inactivation & ELISA VP7) are currently combined, for the BTVPUR AlSap 2-4 vaccine, with a challenge in sheep. Due to the low number of batches to be produced, this animal test remains feasible, having also in mind that the development of an alternative test to the challenge in sheep would require many more animals without guaranteed results. Therefore, the challenge in sheep performed on a routine basis combined with the antigen quality control tests mentioned above (infectious titre before inactivation & ELISA VP7) was considered by the MAH as appropriate to ensure the potency of the batches to be released.

On the basis of the above the CVMP agreed that the current tests applied on the finished product are relevant to guarantee a consistent quality of production and efficacy in sheep. It was also agreed that the provision of a suitable system for quantifying active ingredient at blending stage should no longer be an obstacle to the conversion of the marketing authorisation from "exceptional circumstances" to normal status. However this issue should remain as a condition of the full marketing authorisation.

2. *Information demonstrating compliance with the Ph. Eur. on hydrochloric acid, concentrated, sodium hydrogen carbonate and neomycin sulphate (used to prepare GMEM/VMM) should be provided. (q.47 from initial "other concerns" in LoQ)*

Proof of compliance with the hydrochloric acid 35% with the European Pharmacopeia (Ph. Eur.) was requested following the submission of responses on the first annual re-assessment. In the second annual re-assessment the data provided did not show the requested compliance. Thus the request for clarification was reiterated for this third re-assessment.

For this procedure the MAH confirmed that the solution of diluted hydrochloric acid which is supplied for this product is not described in the Ph. Eur. The solution is made from concentrated hydrochloric acid and water for injection that are both certified Ph. Eur. compliant by the supplier. The most up-to-date description of the hydrochloric acid solution used by Merial (Part II.C.2.2) was provided, as well as a currently valid certificate of analysis for hydrochloric acid 35% (1M solution). A comparative table has also been presented, showing the requirements of the Ph. Eur. monograph 0002, and the tests/limits of acceptance applied by the supplier.

The provided information was satisfactory and this point is now considered as resolved.

3. *Study Report on overdose safety study in calves: As the overdose study should normally be conducted using samples taken from final lots of a test product, the marketing authorisation holder must confirm that the batch of vaccine used in this study is fully representative of current production batch. - Any relevant aspect of the outcome of this study (e.g. size and duration of local reactions, swelling of the draining lymph node, etc.) should be better reflected in relevant sections of SPC (e.g. 4.6 and 4.10). (q.76 from initial "other concerns" in LoQ)*

The MAH provided data to respond to the initial concern as stated above in the previous two annual re-assessments. In the second annual re-assessment the CVMP had concluded that the longer duration of the local reaction following the administration of an overdose, although not really a consequence of normal practice provides additional information sufficiently significant to justify its inclusion in section 4.10 of SPC. The MAH was requested to include this information in section 4.10 of SPC during the third annual re-assessment.

The MAH clarified that the information which was submitted in the previous two annual re-assessments regarding the longer duration of local reactions was based upon the evaluation of the safety study was performed in calves, which is not a target species for BTVPUR ALSAP 2-4. It is thus not relevant to include results from this study in the SPC. Safety studies conducted in sheep showed that an overdose administration of a monovalent BTV-4 induced no abnormal or significant general reaction, and only limited local reactions in compliance with what is already mentioned in the SPC, in terms of severity and duration. An administration of a single dose and repeated dose with high payload of bivalent BTV-2 and BTV-4 in sheep induced local reactions that are also in line with the warning included in the SPC. Other safety studies after the administration of an overdose of vaccine including different BTV serotypes in sheep showed similar results.

The above were acceptable and thus there is no reason to include additional information in section 4.10 of SPC. The point is considered as resolved.

Conclusion on 2nd specific obligation

The provided information on the compliance of hydrochloric acid 35% with the Ph. Eur. and on the duration of local reactions after an overdose was considered acceptable.

An update of part II.C.3 to change the name of one adult bovine serum supplier was provided.

All remaining points under the 2nd specific obligation were considered as resolved besides the implementation of a suitable system for quantifying the active substance at blending. The CVMP agreed that the current tests applied on the finished product are relevant to guarantee a consistent quality of production and efficacy in sheep and the provision of a suitable system for quantifying active

ingredient at blending stage should no longer be an obstacle to the conversion of marketing authorisation to normal status. However such an issue should remain as a condition of the full marketing authorization. On the basis of the above specific obligation 2 is considered fulfilled.

3rd Specific obligation

According to the information available on the European Commission Surveillance network for bluetongue web site (http://www.eubtnet.izs.it/btnet/), outbreaks of BTV serotype 4 between May 2011 and February 2012 were reported in European countries (Cyprus and Greece). Various other sources (i.e. OIE website) confirmed new outbreaks of bluetongue disease in 2013, such as outbreaks of BTV-1 in Italy (Lazio and Toscana regions) and BTV-4 in Palestinian Territories. Other outbreaks of BTV serotype 4 have been reported Spain (http://www.europasur.es/article/comarca/1631263/la/junta/detectacuatro/focos/lengua/ az ul/tarifa/y/castellar.html), in Italy (Sardegna), and in Portugal. Recent outbreaks of BTV- 1 have been reported in France (Corsica).

A risk assessment of the use of the vaccine was presented in the latest PSURs covering the periods June-November 2012 and December 2012-May 2013. On the basis of these, no update of the SPC and product literature was considered necessary.

No updated risk assessment was provided. Despite the absence of this, as a consequence of the recent epidemiological situation in Europe as described above and the previously assessed PSURs, the CVMP confirmed the need to maintain the marketing authorisation of BTVPUR ALSAP 2-4 in the European Union. The third specific obligation is therefore considered fulfilled.

4th Specific obligation

Two PSUR reports (covering periods 01 June 2012 to 30 November 2012 and 01 December 2012 to 31 May 2013) have been submitted since the last annual reassessment. On the basis of the submitted pharmacovigilance information no adverse events occurred worldwide and thus no update of the SPC and product literature was necessary due to safety concerns. The next PSUR was submitted before the end of January 2014 and covers the period between 01 June and 30 November 2013.

The above were considered satisfactory confirming an acceptable safety profile for the product. Moreover the available information so far can be considered suitable in order to allow for the MA provided under exceptional circumstances to be converted to a normal status.

Considering the pharmacovigilance data submitted for this vaccine so far, it was recommended that the periodic PSUR cycle would be re-started for submission of 6 -monthly reports (covering all authorised presentations of this product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at three-yearly intervals.

The fourth specific obligation is considered fulfilled.

2.2. Summary and Conclusions

In accordance with Article 39 of Commission regulation (EC) No. 726/2004, the MAH, Merial, submitted to the European Medicines Agency on 9 December 2013 an application for the third annual re-assessment of the marketing authorisation for BTVPUR AlSap 2-4. Associated to the current annual re-assessment application, the MAH proposed the conversion of the given authorisation to a normal marketing authorisation status. During the current procedure, the four specific obligations were addressed by the MAH.

The two recommendations of the 1st specific obligation were addressed satisfactorily. Regarding the product's stability the data provided were suitable to confirm the 18 months shelf life (as package for

sale) for the three presentations of the BTVPUR Alsap 2-4 vaccine. In relation to the vaccine's DoI the provided studies performed with the monovalent BTV2 and BTV4 vaccines respectively were acceptable to confirm the 12 months duration of immunity for the BTVPUR Alsap 2-4 product. Specific obligation 1 can therefore be considered fulfilled.

Under the 2nd specific obligation all remaining points were considered as resolved besides the implementation of a suitable system for quantifying the active substance at blending. The CVMP agreed that current tests applied on the finished product are relevant to guarantee a sufficient control of the active substance providing consistent quality of production and efficacy in sheep. The provision of a suitable system for quantifying active ingredient at blending stage should no longer be an obstacle to the conversion of marketing authorisation from "exceptional circumstances" to normal status. However such an issue should remain as a condition of the full marketing authorization. On the basis of the above specific obligation 2 is considered fulfilled.

Despite the absence of an updated risk assessment, as a consequence of the evaluation of the recent epidemiological situation in Europe and the PSUR information, the CVMP confirmed the need to maintain the marketing authorisation of BTVPUR ALSAP 2-4 in the European Union and the safe use of the product in the field. The third specific obligation was therefore considered fulfilled.

Two PSUR reports (covering periods 01 June 2012 to 30 November 2012 and 01 December 2012 to 31 May 2013) were assessed since the last annual reassessment. The pharmacovigillance information showed that no adverse events occurred worldwide and thus no update of the SPC and product literature was necessary due to safety concerns. The above confirmed an acceptable safety profile for the product. Moreover the available information was considered suitable in order to allow for the MA provided under exceptional circumstances to be converted to normal status. Considering the pharmacovigilance data submitted for this vaccine so far, the PSUR cycle would be re-started for submission of 6- monthly reports (covering all authorised presentations of this product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at three-yearly intervals.

On the basis of the above the CVMP concluded that all specific obligations have been fulfilled besides point 1 of the 2nd specific obligation. For the MA to convert to normal status as requested by the MAH a condition is needed to ensure the implementation of a quantification test for the active substance at blending as soon as feasible.

3. Benefit-risk assessment

BTVPUR AlSap 2-4 is an inactivated vaccine against bluetongue serotypes 2 and 4. 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 third annual re-assessment.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of the product is prophylactic immunisation to protect sheep against infection with BTV serotypes 2 and 4. The objective is to stimulate active immunity in sheep from 1 month of age in naive animals (or from 2.5 months of age in young animals born to immune sheep) against bluetongue virus serotypes 2 and 4 in order to prevent viraemia and reduce clinical signs associated with the vaccine's BTV serotypes. The vaccine has been proven to prevent viremia and reduce clinical signs due to BTV serotypes 2 and 4.

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

Pharmacovigilance data did not indicate a lack of efficacy in the field and therefore the benefits remain the same.

Additional benefits

BTVPUR AlSap 2-4 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 demonstrated for both serotypes of the vaccine.

The effect of maternally derived antibodies has been investigated and the efficacy of the vaccines in animals from 2.5 months has been shown.

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

3.2. Risk assessment

Main potential risks:

For the target animals:

- Vaccination may be followed by a small local swelling at the injection site (at most 24 cm^2) for a short period (at most 14 days). A transient increase in body temperature, normally not exceeding an average of 1.1°C, may occur within 24 hours after vaccination.

  Pharmacovigillance 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. 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 its 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. Accordingly, the withdrawal period is set at zero days. 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 third annual re-assessment, no further specific risks have been identified from the use of the product; however in view of the potential for the conversion of the MA from exceptional circumstances to normal status the following have been identified:

1. Absence of a suitable system for quantifying active ingredient at blending stage:

A number of tests are used to quantify the active ingredient and provide consistency of the antigen production process (e.g infectious titre before inactivation, VP7 quantification by ELISA,)

These current tests applied on the finished product were considered relevant to guarantee a sufficient control of the active substance providing consistent efficacy in sheep. The provision of a suitable system for quantifying active ingredient at blending stage should no longer be an obstacle to the conversion of marketing authorisation from exceptional circumstances to normal status. However such an issue should remain as a condition of the full marketing authorization. The pharmacovigilance data have not showed any evidence of lack of safety or efficacy supporting the consistency of production.

2. Stability of the product

Data to support a shelf life as package for sale of 18 months for batches of finished product for the 10, 50 and 100 ml presentations were provided. The pharmacovigilance data have not showed any evidence of lack of safety or efficacy thus supporting the stability profile 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. For the conversion of the MA to a normal status a condition should be included in the authorisation for the provision of a suitable system for quantifying active ingredient at blending stage as soon as feasible .

The PSUR cycle for the product will re-start to ensure more frequent pharmacovigilance monitoring following conversion of the MA status.

3.3. Evaluation of the benefit-risk balance

BTVPUR AlSap 2-4 has been shown to have a positive benefit-risk balance for in sheep.

The formulation and manufacture of the product are well described and specifications are supported. Suitable tests ensure a consistent batch quality at final product stage. The implementation of a suitable system for quantifying active ingredient at blending stage should no longer be an obstacle to the conversion of marketing authorisation from exceptional circumstances to a normal status. However the Committee agreed that this issue should remain as a condition of the full marketing authorization. The 18 months of shelf life (as package for sale) and the 12 months of DoI were confirmed.

The product has been shown to be efficacious for the indication of active immunisation of sheep to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotypes 2 and 4.

The pharmacovigilance data have not showed any evidence of safety concerns or lack of efficacy, therefore supporting the consistency of production and also the stability profile of the vaccine.

BTVPUR AlSap 2-4 is well tolerated by the target animals and presents a very low risk for users, the consumers 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.

4. Overall conclusions of the evaluation and recommendations

On the basis of the documentation submitted for evidence of compliance with the specific obligations and for re-assessment of 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.

Besides recommendation 1 of the 2nd specific obligation, the specific obligations have been resolved.

In view of the fact that specific obligations have been fulfilled and remaining concerns are addressed by a condition for the implementation of a suitable system for quantifying the active ingredient at blending stage as soon as feasible, there are no remaining grounds to maintain the marketing authorisation for this product under exceptional circumstances and thus the CVMP recommends the conversion of the marketing authorisation to a normal status.

The CVMP also considered it necessary to restart the PSUR cycle for this product according to the standard rules following the conversion of the marketing authorisation to a normal status. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 May 2014.

4.1. Changes to the community marketing authorisation

Changes are required in the following annex of the Community marketing authorisation:

- Annex I, II and III

5. List of conditions to be included in the full marketing authorisation

1. The marketing authorization holder should provide a suitable system for quantifying active ingredient at blending stage as soon as possible.

2. The CVMP also agreed that the Periodic Safety Update Report (PSUR) cycle should be re-started for submission of 6- monthly reports (covering all authorised presentations of this product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at three-yearly intervals.