EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

**Committee for Medicinal Products for Veterinary Use**

# CVMP assessment report for annual reassessment for BTVPUR AlSap 8

## (EMEA/V/C/146/S/0008)

**Bluetongue virus serotype 8 antigen**

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



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# Product profile

| | |
|---|---|
| Invented name: | **BTVPUR AlSap 8** |
| Active substances: | Bluetongue virus serotype 8 antigen |
| Pharmaceutical form: | Suspension for injection |
| Strength: | ≥ 2.1 log10 pixels* |
| Route of administration: | Subcutaneous use |
| Target species: | Cattle, Sheep |
| Therapeutic indication: | Active immunisation of sheep and cattle to prevent infection, viraemia and reduce clinical signs caused by the bluetongue virus serotype 8. |
| ATCvet code: | QI02AA08 (CATTLE), QI04AA02 (SHEEP) |
| Pharmaco-Therapeutic Group: | IMMUNOLOGICALS |
| Applicant: | MERIAL |

* Antigen content (VP2 protein) by immuno-assay

# 1. Introduction

The manufacturing authorisation holder (MAH) submitted to the European Medicines Agency on 10 February 2012 an application for the annual re-assessment for BTVPUR AlSap 8 and requested that the marketing authorisation (MA) of the vaccine, currently under exceptional circumstances converts to a normal MA in case all the specific obligations in the opinion of the authorisation under exceptional circumstances of BTVPUR AlSap 8 are considered as fulfilled. This is the third annual re-assesment of the product and the CVMP opinions on the previous two were adopted on 14 April 2010 and 4 May 2011 respectively.

The CVMP adopted an opinion and CVMP assessment report on 13 June 2012.

On 3 September 2012, the European Commission adopted a Commission Decision for this application.

## *1.1 Scope of the annual reassessment*

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

1. The Applicant is required 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.

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 Update Safety reports 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.

In the case that all specific obligations and points for concerns (either major objections or other concerns subject to which, the granting of a MA under exceptional circumstances was provided) are considered resolved, then the MA which is currently under exceptional circumstances can convert to standard status.

### *1.2 Documentation submitted*

The marketing authorisation holder submitted the following documentation:

- Answers to the letter of Specific Obligations
- Answers to EMA remaining points of concern
- Answers to the commitment at the last annual re-assessment

### *1.3 Steps taken for the assessment of this annual reassessment*

- The application for the third annual re-assessment was submitted on 10 February 2012.
- The procedure started on 15 February 2012.
- A List of Questions was adopted on 12 April 2012.

## 2. Scientific discussion

### *2.1 Specific Obligations*

***1st specific obligation:***

In order to address the first specific obligation (action plan for remaining outstanding points) an action plan was submitted by the MAH on 11 September 2009 and approved by CVMP on 17 September 2009. The answers to the minor questions that require resolution in order for the authorisation to convert to standard status were submitted on 28 January 2010 and were evaluated by the CVMP on April 2010 as part of the first annual re-assessment. A number of points still remained outstanding in the corresponding CVMP assessment report and were mostly addressed as part of the second re-assessment and approved on 4 May 2011.

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

Stability of the vaccine

*Stability of the 50ml and 100 ml polypropylene bottles*

Final data relevant to stability concerns of the 50 ml and 100 ml polypropylene bottles were submitted relating to:

- 12-months, 18-months and 24 months stability for the 50 ml polypropylene bottle presentations. As complementary information, the certificates of analysis of the 3 batches included in the stability study relating to the 50 doses presentation were provided.

- 18-months and 24-months stability for the 100 ml polypropylene bottle.

**CVMP conclusion**

Overall, the final stability results obtained for up to 27 months of storage at +5°C ±3°C, protected from light, established a positive stability profile for the 50 and 100ml polypropylene vial presentations of BTVPUR AlSap 8 vaccine for the time period monitored. Therefore a final 24 months stability for the 50 and 100 ml polypropylene vial presentations was satisfactorily supported.

*Stability of the 10 ml glass bottles*

- the 12-month stability results for the 10 ml glass bottle presentation were provided. As complementary information, the manufacturing batch protocols (MBP) of the three batches included in the stability study relating to the 10 doses presentation of the vaccine were also submitted.
- The results concerning the 18 months stability for the 10 ml glass bottle presentation, in accordance to the defined specific obligations and the approved timetable were further provided.

**CVMP conclusion**

Overall, the results obtained for up to 21 months of storage at +5 °C ± 3 °C, protected from light, were satisfactory in relation to the stability of the 10 doses glass vial presentations of BTVPUR Alsap 8 and allowed to establish an 18 months stability for those presentations.

Duration of immunity

Two final reports, regarding the duration of immunity of the vaccine in cattle were provided and their conclusions were considered acceptable (study reports titled: Duration of immunity of a BTV8 vaccine administered in 2 injections, 3 weeks apart, to young cattle and Assessment of protection against a BTV-8 challenge, 6 and 12 months after vaccination).

**CVMP conclusion**

The complete results of the two above studies supported a 12 months duration of immunity for cattle. The MAH had already addressed the relevant issue for sheep, where a 12 month duration of immunity was shown following a two injection schedule protocol. As a result the SPC can be updated accordingly to indicate that the duration of immunity is one year and the revaccination schedule should be performed annually for both species.

Maternally derived antibodies (MDAs)

In the absence of any valid conclusions on the impact of MDAs on the vaccine uptake, the limit of 2.5 months of age was considered by CVMP as arbitrary and needed to be further justified. This was of particular importance for sheep.

To address the above the MAH provided results from two studies: an assessment of the serological response of lambs vaccinated with BTVPUR AlSap 8 at different ages, in the presence of maternal antibodies and on the efficacy of BTVPUR AlSap 8 in the presence of maternal antibodies in lambs vaccinated at different ages against a BTV8-8 challenge.

**CVMP conclusion**

The results obtained indicated that in the presence of MDAs, the vaccination of lambs from 2.6 months of age allows an appropriate balance between susceptibility to BTV and receptivity to vaccination. The minimum age for vaccination of lambs born to immune sheep claimed by the applicant as mentioned

above was 2.5 months, which when compared to 2.6 months investigated in the presented studies should not result in major differences; thus it was acceptable to remain in the SPC as such.

The applicant had already addressed the relevant point for cattle providing data that supported the claimed minimum age at vaccination (2.5 months).

***2nd specific obligation:***

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 six new outbreaks of BTV serotype 8, between May 2010 and July 2011 in Europe. These outbreaks illustrated that this serotype remains a potential threat for European countries. In 2011 the risk factors increased with regards to the possible emergence of new Bluetongue outbreaks in Europe as there was an exceptionally hot and dry spring and the seasonally vector-free period was shortened by 2 to 8 weeks in most of the western and southern countries (when compared to 2010) (source: http://ec.europa.eu/food/animal/diseases/controlmeasures/bluetongue_en.htm). In addition, vaccination being no longer mandatory in some countries, allowed 1-2 years old ruminants without immune protection to be in contact with the vector.

**CVMP conclusion**

The above were considered satisfactory and the updated benefit/risk balance justified the maintenance of the product in the EU market.

***3rd specific obligation:***

In order to address point 3 of specific obligations (requirement for submission of frequent PSUR reports with specified monitoring for particular adverse events) two PSURs (4th and 5th) were submitted in the context of this procedure including a risk assessment of the use of the vaccine covering the periods 01 October 20010 to 28 February 2011 and 01 March to 30 September 2011. The reports included monitoring data from adverse events that occurred worldwide following the use of the product, including reporting of the particular specific events indicated in the third specific obligation including abortions, spontaneous death, effects on milk production, local reactions, pyrexia, lethargy and hypersensitivity reactions, including severe allergic reactions. The information presented in those reports was exhaustive, compliant with the specific obligation requirements and did not indicate the need to update the SPC on safety grounds.

In 2011, a large amount of doses of BTVPUR ALSAP 8 were sold, exclusively in the European Union.

4th PSUR covering 01 October 20010 to 28 February 2011

In the period between 1 October 2010 and 28 February common signs of serious adverse events(AEs) observed were injection site abscess or haemorrage, lethargy, anorexia/hyperthermia, hypersalivation, death. Non serious advert events involved temporary appearance of local or systemic reactions (injection site or anaphylactic reactions). The overall worldwide incidence of animals which experienced an AE in the reporting period was approximately 0.016% which was considered acceptable and supported the safety profile of the product in the field.

5th PSUR covering 01 March to 30 September 2011

In the reported period, the most common serious adverse events were associated with systemic disorders, reproductive system disorders, mammary and neurological disorders. The main clinical signs which were recorded in the observed AEs were abortion, anorexia, ataxia, death, milk production decrease. The outcome of the non serious AE also occurring in bovines, was consistent with local injection site reactions described in the SPC. The overall worldwide incidence of animals which experienced an AE in the reporting period was approximately 0.032% which was considered acceptable and supported the safety profile of the product in the field.

The next PSUR has been submitted at the end of May 2012 and covers the period between 01 Oct 2011 and 31 Mar 2012. The frequency of submissions of PSUR reports will remain 6-monthly until the conversion to a full marketing authorisation.

**CVMP conclusion**

It was considered 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 pharmacovigillance data submitted for BTVPUR AlSap 8 for the years 2010 and 2011 it was recommended that the submission of future PSURs should follow the standard timetable, following the conversion of the MA.

## Other concerns

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) and efficacy (i.e validation of challenge models) parts of the dossier remained to be resolved following the last annual reassessment. The detailed assessment of these points was provided and they were all satisfactorily addressed.

## *2.2 Summary and Conclusions*

The MAH submitted on 10 February 2012 an application for the annual re-assessment of BTVPUR AlSap 8 vaccine. This is the third re-assessment since the authorisation of the vaccine on 17 March 2009 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 third annual re-assessment the evidence of compliance against the specific obligations described in the beginning of the report was investigated (section 1.1.1). 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 and efficacy issues which remained outstanding following the last annual reassessment were also addressed. The detailed assessment of these remaining points was provided.

In the context of the third annual re-assessment for BTVPUR AlSap 8 the main issues addressed were the following: the duration of immunity for cattle was shown to be 12 months. The stability for the 50 ml, 100ml polypropylene and the 10 ml glass vials was established to be 24 and 18 months respectively. As a result the shelf life in the SPC was updated accordingly. The effect of maternally derived antibodies was also investigated justifying the efficacy of the vaccine in animals from 2.5 months of age. 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. Results also supported the stability of the active substance for up to 36 months storage. Finally the BTV2 and BTV4 challenge strains used in efficacy trials were shown to have undergone sufficient standardisation to allow the validity of the challenge models used in these studies.

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 October 2010 to 28 February 2011 and 01 March to 30 September 2011. 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 8 under exceptional circumstances. Considering the pharmacovigilance data submitted for BTVPUR AlSap 8 for the years 2010 and 2011 it is recommended that the submission of future PSUR should follow the standard timetable, following the conversion of the MA.

## Benefit-risk assessment

### *2.3 Evaluation of the benefit-risk balance*

**Introduction**

BTVPUR AlSap 8 is an inactivated vaccine against bluetongue serotype 8. The vaccine is formulated to contain aluminium hydroxide and saponin as an adjuvant system. The product has been authorised in 2009 under exceptional circumstances due to the epidemiological situation at the time. This is the third 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.

**Benefit assessment**

**Direct therapeutic benefit**

BTVPUR AlSap 8 is a vaccine containing inactivated serotype 8 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 8.

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

The objective is to induce sufficient immunity to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotype 8.

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 8.

**Additional benefits**

BTVPUR AlSap 8 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 cattle and sheep.

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 both sheep and cattle, which is valuable during a widespread vaccination programme usually necessary to control the spread of disease.

**Risk assessment**

Main potential risks:

For the target animals:

- For sheep and cattle vaccination may be followed by a small local swelling at the injection site (at most 32 $cm^2$) 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. 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 third 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.

**Evaluation of the benefit risk balance**

BTVPUR AlSap 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 8.

The formulation and manufacture of BTVPUR Alsap 8 are well described and specifications are supported. The applicant 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 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 8 under exceptional circumstances.

# 3. 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. Since all the specific obligations have been fulfilled, the CVMP considers that there are no remaining grounds to maintain the marketing authorisation of BTVPUR AlSap 8 under exceptional circumstances.

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

## *3.1. 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).