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EMA/427355/2018
Committee for Medicinal Products for Veterinary Use

CVMP type II variation assessment report for BTVPUR (EMEA/V/C/002231/II/0010)

Common name: Bluetongue vaccine (inactivated) (multi-strain: 1-2 strains out of a set of 3)

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant), submitted to the European Medicines Agency (the Agency) on 3 October 2017 an application for a type II variation for BTVPUR.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.II.4	C.II.4 - Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue	II

The variation is to add BTV serotype 2 to the BTVPUR multi-strain dossier (1, 4, 8) for sheep and cattle.

Current	**Proposed**
Multi-strain dossier for BTVPUR for sheep and cattle Strains included: BTV1 BTV4 BTV8	Multi-strain dossier for BTVPUR for sheep and cattle Strains included: BTV1 **BTV2** BTV4 BTV8

The variation also introduces changes to the Summary of Product Characteristics (and other product information).

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

A Type II variation for the addition of BTV serotype 2 to the BTVPUR multi-strain dossier has been submitted to the European Medicines Agency.

In accordance with the Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD) (EMA/CVMP/IWP/105506/2007), the marketing authorisation holder (MAH) proposes to add the BTV2 serotype to the multi-strain dossier using the available information from the BTVPUR AlSap 2-4 dossier for sheep, which had been authorised under exceptional circumstances according to the recommendations of the CVMP Guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue (EMEA/CVMP/IWP/220193/2008). The MAH proposes to use the information from the BTV multi-strain dossier for sheep and cattle in this variation application. In a previous variation to add BTV4 to the multi-strain dossier, there were cross-references to relevant and previous documentation to fulfil the requirements for quality, safety and efficacy, and this variation application therefore includes similar cross-references. Nevertheless, and according to section 7 of the Guideline for multi-strain dossiers, additional quality and efficacy data have been provided, relating to the batch potency test and efficacy in cattle.

2.1. Quality

Regarding the composition of the vaccine, the applicant has included an update of this section. The applicant has also confirmed that the same maximum number of antigens will be included in the final vaccine formulation (that is, two antigens), with the objective of ensuring faster production of the vaccine.

With respect to the method of preparation of the finished product, the applicant has included an update of this section, including the specification for BTV2 antigen with respect to its titre prior to inactivation.

Sufficient validation of the Qdot Blot technique for detection of the VP2 antigen content of BTV2 has been presented.

With respect to the BTV2 serotype and its inclusion to the multi-strain vaccine dossier, the history of the original strain and the method of preparation of the antigen were provided in the BTVPUR AlSap 2-4 dossier. All the information regarding the seed purity testing, inactivation kinetics and titration are valid for this variation application and no additional studies are therefore necessary.

The blending of the multi-strain vaccine is standardised. With respect to the active ingredients, the volume of each one takes into account the concentration factor, and also that a suspension of bulk antigen containing an equivalent of a pre-defined fixed amount of volume of each serotype must be supplied for 1 ml of dose. The control tests on the BTV2 active ingredient during production have been performed as described in the BTVPUR AlSap 2-4 dossier.

The control tests on the finished product include the specifications for the BTV2 serotype:

- Titre before inactivation (Tech. M.BTV130.R): the limit of acceptance is increased to 7.1 $\log_{10}$ $CCID_{50}$/dose.
- ELISA VP7 content (Tech. 200005): the limit of acceptance for this control test remains unchanged at ≥ 1.0 $\log_{10}$ OD50/ml.

- VP2 protein content (Tech. 200397): the limit of acceptance for this control in the final product batch has been established at 1.82 $\log_{10}$ pixels/dose. With respect to the active ingredient, the limit of acceptance of BTV2 is set at 1.22 $\log_{10}$ pixels/ml culture (non-concentrated) in order to ensure at least 1.82 $\log_{10}$ pixels per vaccine dose.
- Rat serology test (Tech. 002248): The qualitative serological threshold has been established at ≥ 1.8 $\log_{10}$ SN.U.

Appropriate validation of all these techniques has been submitted.

With respect to the stability tests, the stability period was determined for BTVPUR AlSap 2-4, which is the authorised bivalent vaccine, and it was satisfactorily demonstrated to be 18 months for all presentations (see Doc. 2013 annual re-assessment Ref. BT/LCM.13.D816). The applicant therefore proposed a shelf-life for the multi-strain vaccine of 18 months if the multi-strain vaccine contains the BTV2 serotype, whether it is present as a monovalent or a bivalent vaccine. No further stability studies were therefore required. However, in the future if the applicant wishes to increase the shelf-life of BTV2 serotype and its combinations to 24 months, additional stability data would be required. A shelf-life of 18 months for BTV2 (whether in a monovalent or bivalent formulation) is accepted.

In conclusion, information on the development, manufacture and control of the new proposed active substance (BTV2) and the finished product have been presented in a satisfactory manner. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2. Safety

In the context of the Guideline for multi-strain dossiers (EMA/CVMP/IWP/105506/2007), the safety studies submitted for BTVPUR AlSap 1-8 (later converted into BTVPUR multi-strain vaccine) are considered to adequately demonstrate the safety of the BTV2 serotype. These studies previously justified the safety for the bivalent BTVPUR AlSap 1-8 vaccine, and were also considered valid to support the safety of the BTV4 serotype (for the addition of BTV4 serotype to the multi-strain dossier). Furthermore, some of these studies included BTV2 serotype.

All the referred safety studies from the BTV multi-strain dossier were performed in both of the target species (sheep and cattle), and used the recommended route of administration (subcutaneous). The animals used were at the proposed minimum age (approximately one month old for each of the species), and the studies also included pregnant females. Furthermore, the antigen content included in the vaccines used was above the maximum payload fixed for the antigens. Thus, the proposal of the applicant for not including any additional studies to support the safety for the addition of BTV2 serotype to the multi-strain dossier was considered acceptable.

2.3. Efficacy

According to the Guideline for multi-strain dossiers (EMA/CVMP/IWP/105506/2007) section 5.3, the efficacy claim of the multi-strain vaccine corresponds to the sum of the claims of each antigen included in the vaccine.

In this Type II variation application for BTVPUR multi-strain vaccine the applicant applied for the following claims for efficacy:

SPC Section 4.2 Indications for use:

Active immunisation of sheep and cattle to prevent viraemia* and to reduce clinical signs caused by bluetongue virus serotypes 1, 4 and/or 8 (combination of maximum 2 serotypes).

*(below the level of detection by the validated RT-PCR method at 3.68 log_{10} RNA copies/ml, indicating no infectious virus transmission)

Onset of immunity has been demonstrated 3 weeks after the primary vaccination course.

The duration of immunity for cattle and sheep is 1 year after primary vaccination course.

SPC Section 4.9 Amounts to be administered and administration route:

Apply usual aseptic procedures.

Shake gently immediately before use. Avoid bubble formation, as this can be irritating at the site of injection. The entire content of the bottle should be used immediately after broaching and during the same procedure. Avoid multiple vial broaching.

Administer one dose of 1 ml subcutaneously according to the following vaccination scheme:

- Primary vaccination

In sheep:

- First injection: from 1 month of age in naive animals (or from 2.5 months of age in young animals born to immune sheep).
- Second injection: after 3–4 weeks.

  For a monovalent vaccine containing an inactivated Bluetongue Virus serotype 2 or 4, one injection is sufficient.

In cattle:

- First injection: from 1 month of age in naive animals (or from 2.5 months of age in young animals born to immune cattle).
- Second injection: after 3–4 weeks.

- Revaccination

Annual.

During the procedure the indication was revised to the following:

SPC Section 4.2 Indications for use:

Active immunisation of sheep to prevent viraemia* and to reduce clinical signs caused by bluetongue virus serotypes 1, 2, 4 and/or 8 (combination of maximum 2 serotypes).

Active immunisation of cattle to prevent viraemia* caused by bluetongue virus serotypes 1, 2, 4 and/or 8, and to reduce clinical signs caused by bluetongue virus serotypes 1, 4 and/or 8 (combination of maximum 2 serotypes).

*below the level of detection by the validated RT-PCR method at 3.68 log_{10} RNA copies/ml, indicating no infectious virus transmission.

Onset of immunity has been demonstrated 3 weeks (or 5 weeks in sheep for BTV2) after the primary vaccination course for BTV1, BTV2 (cattle), BTV4 and BTV8 serotypes.

The duration of immunity for cattle and sheep is 1 year after primary vaccination course.

2.3.1. Onset and duration of immunity

Sheep

In line with the multi-strain guideline, and also with the already approved variation to add serotype 4 to the multi-strain dossier, it was accepted that the efficacy of the BTV2 antigen in sheep has been demonstrated in the documentation of the already authorised BTVPUR AlSap 2-4 vaccine (Doc 07.0506.R-virulent challenge), by the subcutaneous route and using the proposed scheme of vaccination for this vaccine: one primary injection and then an annual revaccination.

The onset of immunity (OOI) of BTVPUR AlSap 2-4 was established at 3 weeks for BTV4 and at 5 weeks for BTV2 after the primary vaccination course, and the duration of immunity (DOI) was established in sheep for one year after the primary vaccination course (see Annual re-assessment of BTVPUR AlSap 2-4, EMEA/V/C/000139/S/0004).

The interference of maternally derived antibodies has been taken into account in young animals born to immune sheep, through vaccination from 2.5 months of age rather than 1 month of age.

Cattle

BTVPUR AlSap 2-4 is a vaccine authorised only for sheep. For this reason, the applicant included a new efficacy study performed in cattle of the minimum age from 1 month. The new study was carried out to test the efficacy of an inactivated BTV2 vaccine administered in two injections to calves, and then assessed by a virulent BTV2 challenge on day 42. The BTV2 vaccine prevented viraemia but no reduction of clinical signs was observed.

The OOI was demonstrated 3 weeks after the primary vaccination course for BTV2 in cattle.

With respect to the DOI of the BTV2 vaccine in cattle, a study is in progress and the results (by challenge) are expected by April 2019. In the meantime, a serological follow-up is being carried out in vaccinated animals based on the measurement of BTV2 seroneutralising antibodies. The results available to date show an increase in the antibody titre up until about 3 months after the first injection, as was observed with the other serotypes. Thereafter the antibody titre stabilises. The control animals remained seronegative. This validates the results obtained in the vaccinated animals.

The applicant also indicated that the DOI of BTV2 in cattle was supported by studies performed with BTV1 and BTV8 antigens, and also by studies performed with BTVPUR AlSap 2-4 vaccine in sheep. In accordance with previously approved procedures for these vaccines (such as the authorisation of BTVPUR AlSap 1-8 vaccine, and also the addition of serotype 4 to the multi-strain dossier) a DOI study has been initiated to demonstrate (by challenge) in cattle the DOI. Meanwhile, it was considered supportive evidence of the DOI to establish the correlation of the serum neutralisation (SN) antibodies response in cattle between BTV2, BTV4, BTV1 and BTV8 vaccines. This is in line with section 6.3. (Efficacy) of the guideline for multi-strain dossiers (EMA/CVMP/105506/2007). The applicant's commitment to provide the challenge results at 12 months post vaccination is also taken into account in CVMP's consideration therefore one year DOI of the BTV2 component of the vaccine for cattle is supported with the following recommendation:

In view of the performance of the interim study by the applicant, the results of the challenge at 12 months post vaccination in order to confirm the duration of immunity of the BTV2 in cattle would be provided at the end of the study.

Following the efficacy assessment some changes have been included in the corresponding sections of the SPC (and other product information) so they were finalised and agreed as follows:

SPC Section 4.2 Indications for use:

Active immunisation of sheep to prevent viraemia* and to reduce clinical signs caused by bluetongue virus serotypes 1, 2, 4 and/or 8 (combination of maximum 2 serotypes).

Active immunisation of cattle to prevent viraemia* caused by bluetongue virus serotypes 1, 2, 4 and/or 8, and to reduce clinical signs caused by bluetongue virus serotypes 1, 4 and/or 8 (combination of maximum 2 serotypes).

*below the level of detection by the validated RT-PCR method at 3.68 log_{10} RNA copies/ml, indicating no infectious virus transmission.

Onset of immunity has been demonstrated 3 weeks (or 5 weeks in sheep for BTV2) after the primary vaccination course for BTV1, BTV2 (cattle), BTV4 and BTV8 serotypes.

The duration of immunity for cattle and sheep is 1 year after primary vaccination course.

SPC Section 4.9 Amounts to be administered and administration route:

Apply usual aseptic procedures.

Shake gently immediately before use. Avoid bubble formation, as this can be irritating at the site of injection. The entire content of the bottle should be used immediately after broaching and during the same procedure. Avoid multiple vial broaching.

Administer one dose of 1 ml subcutaneously according to the following vaccination scheme:

- Primary vaccination

  In sheep:

  - First injection: from 1 month of age in naive animals (or from 2.5 months of age in young animals born to immune sheep).
  - Second injection: after 3–4 weeks.

  For a monovalent vaccine containing an inactivated bluetongue virus serotype 2 or 4, or for a bivalent vaccine containing both serotypes 2 and 4 together, one injection is sufficient.

  In cattle:

  - First injection: from 1 month of age in naive animals (or from 2.5 months of age in young animals born to immune cattle).
  - Second injection: after 3–4 weeks.

- Revaccination

  Annual.

In conclusion, the data presented with the variation to include BTV2 in BTVPUR vaccine are considered adequate to support an indication for the active immunisation of both sheep and cattle to prevent viraemia (both species) and to reduce the clinical signs (sheep only) caused by bluetongue virus serotype 2.

3. Benefit-risk assessment of the proposed change

BTVPUR multi-strain is an inactivated adjuvanted vaccine against bluetongue disease virus serotypes 1, 2, 4 and 8.

The product is intended for use in sheep and cattle to prevent viraemia and to reduce the clinical signs caused by bluetongue virus serotypes. There is a maximum of 2 serotypes in each vaccine.

The proposed variation is to add BTV serotype 2 to the BTVPUR multi-strain dossier (which currently includes only serotypes 1, 4, 8) for sheep and cattle.

3.1. Benefit assessment

Direct therapeutic benefit

The therapeutic benefit of BTVPUR is its efficacy to induce immunity to prevent viraemia and to reduce the clinical signs caused by bluetongue virus serotypes 1, 2, 4 and/or 8 in sheep and, in cattle, to prevent viraemia caused by bluetongue virus serotype 1, 2, 4 and/or 8, and to reduce clinical signs caused by bluetongue virus serotypes 1, 4 and/or 8.

The OOI is 3 weeks after the primary vaccination for BTV serotypes 1, 4 and 8. For the BTV2 serotype, the OOI after primary vaccination is 3 weeks in cattle and 5 weeks in sheep. The DOI is one year.

Additional benefits

The inclusion of BTV2 serotype in the BTV serotypes that may be used in BTVPUR gives the opportunity for a more rapid production of vaccine in the event of an outbreak of bluetongue in Europe caused by BTV serotype 2.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Information on development, manufacture and control of the new proposed antigen (BTV2) and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Risk for the target animals remains unaffected by this variation. Administration of BTVPUR multi-strain in accordance with SPC recommendations is generally well tolerated.

The safety of BTVPUR multi-strain (including BTV2) in sheep and cattle was confirmed in the applications for the already authorised products BTVPUR AlSap 1-8 and BTVPUR AlSap 2-4.

Risk for the user:

The risk for the user remains unaffected by this variation.

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 there is no risk of the spread of live virus. The adjuvants are not considered to pose a risk

to the environment. Additionally, no special concern is posed by the final product in light of the safety of the 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 of its recommended method for disposal.

Risk for the consumer:

The risk for the consumer remains unaffected by this variation.

No withdrawal period is needed.

Special risks:

No specific risks of the vaccine have been identified.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform of the potential risks to the target animals, the user and the environment and provide advice for reducing these risks.

3.4. Evaluation of the benefit-risk balance

Information on the development, manufacture and control of the active substance and the finished product has been presented and leads to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

4. Conclusion

Based on the original and complementary data presented on quality, and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for BTVPUR can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

- to add BTV serotype 2 to the BTVPUR multi-strain dossier (1, 4, 8) for sheep and cattle.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product with the following recommendation:

> In view of the performance of the interim study by the applicant, the results of the challenge at 12 months post vaccination in order to confirm the duration of immunity of the BTV2 in cattle would be provided at the end of the study.

It is proposed to continue the same periodic safety update report (PSUR) calendar cycle that has been accepted for BTVPUR. The data lock point for the next PSUR would be December 2019 (first triennial PSUR).

Changes are required in the following Annexes to the Community marketing authorisation: I, II, III and IV.