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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Zulvac BTV (EMEA/V/C/004185/II/0004)

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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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, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 7 November 2019 an application for a type II variation for Zulvac BTV.

1.2. Scope of the variation

Variation(s) requested		**Type**
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

This variation aims to vary the existing multi-strain dossier in order to allow the use of the current monovalent vaccine against serotype 4 in cattle. The MAH is taking the opportunity to update the Annex II of the Product Information, in addition to the introduction of the respective Product Information Annex I and Annex III updates to reflect the changes introduced within this variation.

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, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

2.1. Quality

The current variation mainly concerns the addition of cattle as target species for the monovalent BTV-4 vaccine already approved for use in sheep. In cattle, the identical monovalent BTV-4 vaccine as approved for sheep will be used, but a double dose volume (i.e. 4 ml versus 2 ml in sheep) will be administered to cattle. This approach is considered acceptable within the scope of a multi-strain dossier. The use of a larger dose volume has been shown to be both safe and efficacious.

Also, the maximum antigen content for the monovalent BTV-1 and BTV-8 vaccines for use in both sheep and cattle has been increased to the same level as approved for the monovalent BTV-4 vaccine in sheep

(i.e. $10^{8.1}$ tissue culture infective dose 50% ($TCID_{50}$)/2 ml dose). The increased maximum antigen contents have been shown to be safe in both target species (sheep and cattle).

2.2. Safety

From the Good Laboratory Practice (GLP)-compliant study, a single repeated dose administration of Zulvac BTV 1+4 administered intramuscularly to 8 minimum age calves was demonstrated to be safe. Seven calves injected with phosphate buffered saline (PBS) served as controls. No anaphylactic reactions occurred after a single or repeated single dose of a vaccine batch that contained the maximum total BTV antigen amount based on the pre-inactivation titre of two vaccine strains (i.e. BTV-1 and BTV-4). Following the second vaccination, transient temperature increases were noted in 75% of vaccinated animals within 48 hours after vaccination and had a maximum duration of 1 day. Injection site swellings were observed in 75% of the vaccinated animals and persisted for no more than eight days. This is reflected in the SPC.

The animal number in the control group was below the currently recommended number of 8 control animals according to target animal safety (TAS) VICH GL 44. This deviation from the recommendations is however unlikely to change the results and conclusions of the study.

The Good Clinical Practice (GCP)-compliant field safety study (n = 119 Friesian cows) showed that Zulvac BTV serotype 4 administered intramuscularly to cows at different reproductive stages was demonstrated to be safe without adverse effects on milk yield using a vaccine batch that contained a pre-inactivation titre of $10^{8.4}$ $TCID_{50}$/4 mL dose (equivalent to $10^{8.1}$ $TCID_{50}$/2 ml dose).

No vaccine-related abnormal health was observed. Transient temperature increases were commonly seen for 24 hours after vaccination. This is reflected in the SPC. No injection site reactions were detected.

The study design was suitable to detect safety issues and was in accordance with existing recommendations.

In the same GCP-compliant field safety study, Zulvac BTV serotype 4 did not show negative effects on pregnancy rates and gestation length.

Abortion/re-absorption rates were higher in the vaccinated group (3/59) than the control group (1/60), but the temporal association between vaccination and abortion/re-absorption was weak in two of three cases (>40 days). Since the vaccine is inactivated and therefore unable to disseminate to the foetus, it is unlikely that the vaccine caused delayed abortions in these two cases. In the third case, a cow at 56 days of gestation returned to service within a week of the second vaccination. The animal showed no other abnormal clinical signs and no pyrexia to explain the re-absorption.

Considering all available data, the higher abortion rate in vaccinated cows compared to mock-vaccinated cows in the current field study was probably a coincidental finding rather than the reflection of a safety issue.

In conclusion, the respectively GLP and GCP compliant safety studies clearly indicate that a Zulvac BTV serotype 4 vaccine, formulated at maximum antigen content, has a good safety profile when administered as a single or repeated 4 mL dose in 12 weeks old calves or cattle in different physiological stages including lactation and pregnancy.

No changes have therefore been made to the summary of product characteristics (SPC) section 4.7 and package leaflet (PL) section 12 (Use during pregnancy, lactation or lay). However, SPC section 4.9 (amounts to be administered and administration route) and PL section 8 (dosage, route and method of administration) have been revised to reflect the revised administration regime for BTV serotype 4 in cattle.

2.3. Efficacy

Onset of immunity

In the negatively controlled, non GCP-compliant onset of immunity (OOI) challenge study , including in total 19 BTV antibody and BTV genome free calves (3-4 months old), calves (n=12) were inoculated with Zulvac BTV serotype 4 batch (relative potency (RP)=1.0, containing BTV-4 at a pre-inactivation titre of $10^{7.5}$ $TCID_{50}$ per 4 mL dose) or PBS intramuscularly, twice three weeks apart on days 0 and 21. The study showed that Zulvac BTV serotype 4 was efficacious against a virulent heterologous BTV-4 challenge infection that caused viraemia in all control calves. Vaccination prevented viraemia with an onset of immunity of 14 days.

Duration of immunity

In the negatively controlled, non-GCP compliant duration of immunity (DOI) challenge study , including 36 BTV antibody and BTV genome free approximately 3 months old animals, calves were inoculated (4 ml intramuscularly) with or a vaccine batch at RP=1.0 with a titre of $10^{7.2}$ $TCID_{50}$/2 mL dose (group 3), or a vaccine batch at RP=1.3 with a pre-inactivation titre of $10^{7.5}$ $TCID_{50}$/2 mL dose (group 2) or PBS.

The results of the study showed that Zulvac BTV serotype 4 at both potencies, administered intramuscularly three weeks apart to calves around the minimum age, was efficacious against a virulent heterologous BTV-4 challenge infection that caused viraemia in all control calves 6 months after the second vaccination. Vaccination prevented viraemia with a duration of immunity of 6 months. The only notable difference between the two vaccine batches was a faster onset and a higher peak titre of neutralising antibody responses at the higher antigen content following vaccination.

Field studies

The applicant did not perform any field efficacy studies with Zulvac BTV serotype 4. Given the epidemiology of the disease and the indication of the vaccine (prevention of viremia), this is acceptable.

Overall conclusion on efficacy

Zulvac BTV serotype 4 has been demonstrated as being efficacious in preventing viremia in cattle. The onset of immunity is 14 days and the duration of immunity 6 months. No field study has been performed. This is considered as acceptable.

3. Benefit-risk assessment of the proposed change

This product is authorised for the following indications:

Sheep:

Active immunisation of sheep from 6 weeks of age for the prevention* of viraemia caused by bluetongue virus, serotype 1 or serotype 8.

Active immunisation of sheep from 6 weeks of age for the reduction* of viraemia caused by bluetongue virus, serotype 4.

*Below the level of detection of < 3.9 log10 genome copies/ml by the validated RT-qPCR method, indicating no presence of viral genome.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: 12 months after completion of the primary vaccination scheme.

Cattle:

Active immunisation of cattle from 12 weeks of age for the prevention** of viraemia caused by bluetongue virus, serotype 1 or serotype 8.

**Below the level of detection of < 3.4 log10 genome copies/ml by a validated RT-qPCR method, indicating no presence of viral genome.

Onset of immunity: Bluetongue virus, serotype 1: 15 days after completion of the primary vaccination scheme. Bluetongue virus, serotype 8: 25 days after completion of the primary vaccination scheme.

Duration of immunity:

Bluetongue virus, serotype 1: 12 months after completion of the primary vaccination scheme.
Bluetongue virus, serotype 8: 12 months after completion of the primary vaccination scheme.

There is evidence of BTV-1 seroneutralising antibodies indicative of protection for up to 21 months after primary vaccination.

The proposed variation is to vary the existing multi-strain dossier in order to allow the use of the current monovalent vaccine against serotype 4 in cattle. Additionally, the applicant also takes the opportunity to correct a typographical error in part 2.B.2, part 2.E.3 and in the SPC/PI.

3.1. Benefit assessment

Direct therapeutic benefit

The therapeutic benefit of the inclusion of serotype 4 for cattle in Zulvac BTV is its efficacy to induce immunity to prevent viraemia caused by bluetongue virus, serotype 4 in cattle.

Additional benefits

The inclusion of BTV serotype 4 to the pool of BTV serotypes that may be used in Zulvac BTV gives the opportunity for a more rapid production of vaccine in the event of an outbreak of bluetongue in Europe caused by BTV serotype 4, in both sheep and cattle.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Risk for the target animals remains unaffected by this variation. Administration of Zulvac BTV in accordance with SPC recommendations is generally well tolerated. The safety of Zulvac BTV serotype 4 in cattle has been demonstrated. The safety of Zulvac BTV (serotype 1 and 8 in cattle and 1, 4 and 8 in sheep) was confirmed in previous applications for Zulvac BTV.

Risk for the user:

The risk for the user remains unaffected by this variation.

Risk 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 viruses. 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

The product has been shown to be efficacious for the prevention of viremia of BTV4 in cattle. The benefit - risk balance is positive.

4. Conclusion

Based on the original and complementary data presented on safety 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 Zulvac BTV can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008) , as follows:

To vary the existing multi-strain dossier in order to allow the use of the current monovalent vaccine against serotype 4 in cattle. The MAH is taking the opportunity to update the Annex II of the Product Information.

Changes are required in the following Annexes to the Community marketing authorisation:

I, II, IIIA, IIIB and A

Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, sections 2, 4.2, 4.6, 4.9, 4.10, 5, 6.3 and 6.5 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.