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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Circovac (EMEA/V/C/000114/VRA/0020/G)

Vaccine common name: Porcine circovirus vaccine (inactivated)

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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Ceva-Phylaxia Co. Ltd (the applicant), submitted to the European Medicines Agency (the Agency) on 28 March 2022 an application for a group of variations requiring assessment for Circovac.

1.2. Scope of the variation

Variation(s) requested		**Type**
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	VRA_2
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	VRA_2

To extend the duration of immunity for Circovac from at least 14 weeks to at least 23 weeks and to correct the duration of lethargy in the product information from 1 day to 1-2 days.

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 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Circovac is an emulsion and suspension for emulsion for injection containing inactivated Porcine Circovirus 2 (PCV2) (>1.8 log10 ELISA Units/ml). It is intended to induce active immunisation of piglets to reduce faecal excretion of PCV2 and virus load in blood, and as an aid to reduce PCV2-linked clinical signs, including wasting, weight loss and mortality as well as to reduce virus load and lesions in lymphoid tissues associated with PCV2 infection. Moreover, it is intended for the active immunisation of sow and gilts to provide passive immunisation of piglet via the colostrum, to reduce lesions in lymphoid tissues associated with PCV2 infection and as an aid to reduce PCV2-linked mortality.

The onset of immunity currently authorised is 2 weeks after vaccination and the duration of immunity is at least 14 weeks after vaccination.

With this variation the applicant wishes to extend the duration of immunity for Circovac from at least 14 weeks to at least 23 weeks when used alone and to correct the duration of lethargy in the product information from 1 day to 1-2 days when used mixed with Hyogen. The extension of the duration of immunity variation is to fulfil a commitment taken by the applicant in the variation procedure of the associate use of Circovac and Hyogen (EMEA/V/C/WS/1945).

In order to support this change, the applicant has provided a study which objective was to demonstrate a 23-week long duration of immunity against PCV2 virus infection of Circovac alone or mixed with Hyogen in one injection. Three groups of twenty 21-day old piglets, with low-medium level of maternally derived antibodies against PCV2, were vaccinated at 3 weeks as follows: Group 1 not vaccinated; Group 2 vaccinated with Circovac + Hyogen RTM; Group 3 vaccinated with Circovac alone. The PCV antigen content was the minimum piglet dose of Circovac, containing 1.5 $\log_{10}$ ELISA Unit/0.5 ml. All animals were challenged on D161 (23 weeks after vaccination) by intranasally infection with a virulent PCV2 strain. The study ended 27 days after challenge.

Considering that the challenge with PCV2 under laboratory conditions usually does not result in significant clinical signs, different parameters were used to evaluate the efficacy of the vaccine. In particular: viremia; the PCV2 load in at least one of the following lymphoid tissues tonsils, mediastinal, mesenterial and inguinal lymph nodes tested by PCR, immunohistochemistry and histology; virus shedding tested by nasal and faecal swabs; antibody response to PCV2 and body weight gain difference vaccinated and non-vaccinated animals during the post-challenge observation period (measured as secondary parameters).

Real-time PCR was performed to assess the incidence of viremia and to quantify the amount of PCV2 virus (copy numbers/ml) in the sera. Due to the low number of positive animals, even in the control group, no statistically significant difference was found among groups using the Kruskal-Wallis omnibus test.

Real-time PCR was also performed to quantify the amount of PCV2 virus (copy numbers/ml) in tonsils, mediastinal, mesenterial and inguinal lymph nodes on D188. In the tonsils, significant differences were found among groups using the Kruskal-Wallis omnibus test. In the pairwise comparisons, significant differences were found between Group 1 vs. 2 and Group 1 vs. 3. In the mediastinal lymph node no significant differences were found among groups using the Kruskal-Wallis omnibus test. However, in the pairwise comparisons, significant differences were found between Group 1 vs. 2 and Group 2 vs. 3. In the mesenterial lymph node significant differences were found among groups using the Kruskal-Wallis omnibus test. In the pairwise comparisons, significant differences were found between Group 1 vs. 2 and Group 1 vs. 3. In the inguinal lymph node no significant differences were found among groups using the Kruskal-Wallis omnibus test. However, in the pairwise comparisons, significant difference was found between Group 1 vs. 2.

No findings were observed in the tonsils and lymph nodes histological analysis. No significant differences were found among groups using the Kruskal-Wallis omnibus test in the tonsils, mediastinal, mesenterial and inguinal lymph nodes. No statistically significant differences were detected with immunohistochemistry either.

Real-time PCR was also used to quantify the amount of PCV2 virus (copy numbers/ml) in faecal swabs. The results showed no differences among groups. However, in nasal swabs also tested via PCR, significant differences were found among groups using the Kruskal-Wallis omnibus test. In the pairwise comparisons, significant differences were found between Group 1 vs. 2 and Group 1 vs. 3.

Regarding the secondary parameters, body weights were measured at D0 and before challenge, therefore no useful information can be inferred regarding the efficacy of the product.

Antibody response was determined by ELISA. On each time points, on the challenge day and after challenge (D161, D166, D175, D182, D188) PCV2 antibody levels of the vaccinated groups were significantly higher compared to the control group showing a clear serological response against PCV2.

In summary, the vaccinated pigs, compared to the controls, had a significant reduction of the viral load in 4 lymphoid tissues, and a significant reduction of virus shedding (in the nasal swabs).

Regarding the secondary parameters, the body weight is not considered pertinent since no data were recorded after challenge. Conversely, the significant increase in serological response is predictive of the capability of the vaccine to promote a specific immune response. The seroconversion could be a proxy of efficacy taking into consideration that humoral response is considered of some efficacy versus the virus, especially when neutralising antibodies are detected. However, since antibodies were measured by an ELISA test, there is no evidence that the humoral response is also characterised by the production of neutralising antibodies. Therefore, the results of serology cannot be considered conclusive.

Overall, considering the limitation to reproduce the disease in laboratory conditions, especially in animal of 26 weeks of age, and the results provided, it seems reasonable to affirm that the claims proposed are justified and that data support the variation.

Therefore, based on the data submitted, Circovac, at a dose of 1.5 $\log_{10}$ ELISA Units of PCV2 antigen per piglet can be considered efficacious for the investigated duration of immunity of 23 weeks after challenge.

Regarding the proposed new duration of the lethargy when the product is used mixed with the vaccine Hyogen, during the variation of the associated use of Circovac with Hyogen (EMEA/V/C/000114/WS1945/0018) the laboratory safety study DAH12 (report-db-110-2017) was assessed (study also provided in this variation documentation). In one pig, depression had resolved when observed on Day 1 after vaccination. The actual SPC, reporting that lethargy "resolves spontaneously within one day", is misleading because the sign disappeared the second day after vaccination. Therefore, the proposed wording better reflects the data presented and it is considered acceptable.

3. Benefit-risk assessment of the proposed change

Circovac is an emulsion and suspension for emulsion for injection, containing, as active substance, inactivated porcine circovirus type 2 (PCV2) (≥1.8 log10 ELISA Units/ml). The product can be used in gilts, sows and piglets from 3 weeks of age. It is authorised for the active immunisation of piglets to reduce faecal excretion of PCV2 and virus load in blood, and as an aid to reduce PCV2-linked clinical signs, including wasting, weight loss and mortality as well as to reduce virus load and lesions in lymphoid tissues associated with PCV2 infection. It is also authorised for use in sows and gilts to achieve passive immunisation of piglets via the colostrum, after active immunisation of sows and gilts, to reduce lesions in lymphoid tissues associated with PCV2 infection and as an aid to reduce PCV2-linked mortality.

The proposed variation is to extend the duration of immunity for Circovac from at least 14 weeks to at least 23 weeks and to correct the duration of lethargy in the product information from 1 day to 1-2 days.

The extension of the duration of immunity variation is submitted to fulfil a commitment taken during the variation procedure to obtain the associate use of Circovac and Hyogen (EMEA/V/C/WS/1945).

3.1. Benefit assessment

Direct therapeutic benefit

The benefits of the product remain unaffected by this variation.

Additional benefits

The product has a longer lasting effect than the initial product.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety remains unaffected by this variation.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

The product has a longer lasting effect than the initial product.

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, consumer safety, target animal safety.

Based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original data presented on safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Circovac can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows:

to extend the duration of immunity for Circovac from at least 14 weeks to at least 23 weeks and to correct the duration of lethargy in the product information from 1 day to 1-2 days

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.

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

I and IIIB.

As a consequence of these variations, sections list affected sections of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.