15 February 2018
EMA/101056/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Porcilis PCV ID (EMEA/V/C/003942/WS1277(0002))

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 20 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 1 December 2017 an application for a type II variation for Porcilis PCV ID and related nationally authorised products, following a work sharing procedure.

1.2. Scope of the variation

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

To change the SPC/leaflet wording on associated non-mixed use of Porcilis PCV ID and Porcilis M Hyo ID ONCE. The registered associated non-mixed use of these vaccines means that the vaccines can be administered on the same day, at different sites. With this variation the text of the product information of both vaccines will be changed from "at different sites" to "separated by at least 3 cm".

The product information was simultaneously aligned with the latest QRD template.

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

Porcilis PCV ID and Porcilis M Hyo ID ONCE are indicated for vaccination of pigs using an intradermal device (multi-dose needle-free injection device for intradermal application of liquids: “IDAL”). Associated non-mixed use of these two vaccines is authorised, and the use is described as: “can be administered on the same day, at different sites”. In studies performed in support of the original associated non-mixed use claim, animals were vaccinated with the two vaccines simultaneously on opposite sides of the neck or back. This gave rise to somewhat more pronounced local reactions compared to the use of individual vaccines, which is indicated in the products’ SPCs.

A multi-nozzle injection device has been developed which allows simultaneous intradermal vaccination with injection sites spaced 3 cm apart. The variation is, therefore, to replace the product

information text regarding injection sites from "…at different sites.." to "..separated by at least 3 cm".

Three combined laboratory safety and efficacy studies and one field safety study were presented in support of the variation.

The studies provided indicate that systemic reactions are similar when injection sites are spaced 3cm apart or at opposite sides of the animal: clinical signs were not observed and rectal temperature increases remained within the limits already indicated in the SPC's.

Local reactions increased in severity and duration when injections were spaced 3 cm apart: redness and crusts occurred very commonly at both injection sites and the maximum duration increased to 7 weeks (instead of 5) for local reactions at the site of Porcilis PCV ID injection. However the maximum size of the reactions did not exceed those already indicated in the respective SPC's (6 cm) in any of the laboratory or field studies, nor did the duration of the local reactions at the site of Porcilis M Hyo ID ONCE injection.

In conclusion, the associated non-mixed use, with vaccines applied 3 cm apart has an acceptable safety profile when performed in accordance with the product information. The proposed changes to the product information of both products accurately reflect the adverse events observed after associated non-mixed use with injections spaced 3 cm apart.

Efficacy of associated non-mixed use of Porcilis PCV ID and Porcilis M Hyo ID ONCE (when administered at opposite sides of the animal) has been fully evaluated at the time Porcilis PCV ID was first registered. Studies were performed that supported no significant change to Onset and Duration of immunity against both *M. hyopneumoniae* and PCV2 when the associated use was compared to individual vaccinations.

The Guideline on combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010) states that for associated use: "the basis for association of IVMPs should be a demonstration of acceptable safety and absence of serious interference between the IVMPs involved." And: "it should be demonstrated that the association of IVMPs should not negatively affect the onset and duration of immunity as established for the individual IVMPs."

The difference between the two methods of administration in case of associated non-mixed use (on opposite sides or spaced 3 cm apart) is the focus of this variation application. From the results of the studies provided it can be concluded that the onset of immunity is likely not affected by the administration method. Although not all claims were investigated (and thus substantiated), it is considered sufficient in this case that the important parameters reduction of lung lesions (*M. hyopneumoniae*) and the antibody titres (PCV2) were not significantly different.

Efficacy data has not been provided beyond Day 28 for *M. hyopneumoniae* or beyond Day 64 for PCV2. However, based on the existing Duration of Immunity data for associated non-mixed use combined with the absence of observable differences between the two methods of administration there is no reason to expect the duration of immunity to be reduced when injections are spaced 3 cm apart. This reasoning can be accepted: the absence of serious interference is sufficiently supported.

Appropriate updated dossier pages were provided for both Porcilis PCV ID and Porcilis M Hyo ID ONCE. Changes to the product literature of both vaccines have been proposed to include the change in the application method for associated non-mixed use and the resulting adverse (local) reactions and that align the documents with the latest QRD template. These changes are generally acceptable and in accordance with the data provided. In conclusion, the efficacy of both vaccines when administered concurrently, spaced 3 cm apart, is sufficiently supported by the data.

3. Benefit-risk assessment of the proposed change

Porcilis PCV ID emulsion for injection for pigs containing porcine circovirus type 2 ORF2 subunit antigen is for the active immunisation of fattening pigs to reduce viraemia, virus load in lungs and lymphoid tissues and virus shedding caused by PCV2 infection and in addition, to reduce loss of daily weight gain and mortality associated with PCV2 infection. Onset of immunity is 2 weeks after immunisation with duration of 23 weeks.

Porcilis M Hyo ID ONCE emulsion or injection for pigs containing inactivated *Mycoplasma hyopneumoniae* strain 11 is indicated for active immunisation of pigs to reduce pulmonary lesions and the decrease in daily weight gain during the finishing period due to infection caused by *Mycoplasma hyopneumoniae*. Onset of immunity is 3 weeks after immunisation with duration of 22 weeks.

The proposed variation is to change the SPC/leaflet wording on associated non-mixed use of Porcilis PCV ID and Porcilis M Hyo ID ONCE. The registered associated non-mixed use of these vaccines means that the vaccines can be administered on the same day, at different sites. With this variation the text of the product information of both vaccines will be changed from "*at different sites*" to "*separated by at least 3 cm*". The product information is also simultaneously aligned with the latest QRD template.

3.1. Benefit assessment

Direct therapeutic benefit

The direct therapeutic benefits of both products remain unaffected by this variation.

Additional benefits

The proposed change in the description of the associated non-mixed use of Porcilis PCV ID and Porcilis M Hyo ID ONCE from "at different sites" to "separated by at least 3 cm." will allow for the use of a multi-nozzle intradermal injection device (twin IDAL). This in turn allows for a single handling of the animal to apply both vaccines, thereby reducing the stress for the animal.

3.2. Risk assessment

No change to the impact of the product is envisaged on the following aspects: quality and efficacy.

Safety:

Risks for the target animal:

Associated non-mixed use of the vaccines in accordance with SPC recommendations is generally well tolerated. The risk for the target animal of associated non-mixed use separated by at least 3 cm was evaluated in three laboratory and one field (safety) study. The main reported adverse event is a local reaction, consisting of a hard non-painful nodule with a maximum size of 6 cm and a maximum duration of 7 weeks. Redness and crusts at the site of the local reaction are very commonly observed. Warnings concerning local reactions and transient temperature increases have been appropriately adapted in the product literature.

Risk for the user:

The risk for the user is not affected by this variation, since the recommended method of administration (intradermal using the IDAL) does not change. If anything, the risk is reduced since only single handling is required for application of both vaccines.

Risk for the environment:

This variation does not affect the risk to the environment.

Risk for the consumer:

This variation does not affect the risk to the consumer.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of associated non-mixed use when applied 3 cm apart, relevant to the target animal.

Appropriate information has been included in the SPC and other product information to inform on the potential risks on the user, environment and consumer and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

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

Based on the data presented, the overall benefit-risk is deemed 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 Porcilis PCV ID and Porcilis M Hyo ID ONCE can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

With this variation the text of the product information of both vaccines will be changed from *"at different sites*" to "*separated by at least 3 cm*". The product information was simultaneously aligned with the latest QRD template.

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.