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Veterinary Medicines and Product Data Management

EPAR Scientific Discussion post-authorisation update for Circovac type II variation

Scope of variation: addition of piglets as a target category of animals

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1. Background information on the variation

Pursuant to Article 16 of Commission Regulation (EC) No. 1234/2008, the Marketing Authorisation Holder (MAH), Merial S.A.S., submitted to the Agency on 6 April 2010 an application for a Type II variation for Circovac.

2. Scientific discussion

Introduction

Circovac vaccine is currently indicated to vaccinate sows and gilts, in order to protect the progeny through colostrum intake. This category of target animal species has been developed in the face of an emerging epidemic disease. During this early emergency phase, in addition to passive immunity conferred to the next generation of piglets by the vaccination of sows and gilts, many breeders also implemented the vaccination of piglets (an "off-label" use) to quickly decrease the viral load on the farm and to actively protect the piglets present in the premises. The infection of piglets occurs mostly during the first 6 weeks of life, when the immune system of piglets is still maturing. Therefore, by vaccinating gilts and sows, passive immunity is provided to piglets in order to reduce typical lesions caused by porcine circovirus type 2 (PCV2) in lymphoid tissues and as an aid to reduce mortality associated with PCV2 infection. Infection with PCV2 usually occurs in the nursery and to a lesser extent in the post-weaning period. Nevertheless, pigs of various ages can be infected with PCV2 and show typical lymphoid lesions. An increasing number of late occurring PCV2 infections is being observed in animals aged 12-19 weeks. In cases of acute PCV2 associated disease (PCVD) outbreaks, of gathering of animals with unknown origins, or of uncertain colostrum uptake, vaccination of piglets may be a useful tool in the control of the disease. In the MAH's opinion, the addition of piglets as a target category of animal species will be useful in order to cover all epidemiological and field situations relating to PCVD.

Development of the piglet claim

Based upon feedback from the field, the MAH further developed a vaccination claim in piglets. A summary of the antigen content in one dose of the vaccine administered to sows/gilts and to piglets was provided. Given the difference of dose volume to be injected in the two different categories of swine, it was proposed to simplify its expression by using a qualitative and quantitative composition in ml (instead of dose for sows).

All of the trials presented with the submitted variation documentation were conducted in accordance with Directive 2001/82/EC, as amended, and in accordance with GLP and GCP principles under laboratory and field conditions (with the exclusion of supportive field data, for which a data validation statement was provided). Safety has been studied in laboratory conditions at one dose, overdose and repeated doses using the maximum dose at the minimum age of piglets. The basic efficacy studies were performed using the minimum dose. The onset of immunity was demonstrated in specific pathogen free (SPF) piglets whereas the duration of immunity was demonstrated in conventional piglets in the face of maternal antibodies at the time of vaccination. Field trials were completed to confirm the safety and efficacy profiles of the product in piglets under field conditions. In addition, reports were presented of a number of field trials where the vaccine was used in piglets.

Safety of the product

The safety of Circovac has been demonstrated in piglets from 3 weeks old in laboratory and field conditions, at the maximum dose.

Laboratory safety in 3-week old piglets

Studies have been conducted to demonstrate the safety of one dose, repeated doses and overdose of Circovac in piglets. Under the experimental conditions, the use of SPF pigs allowed assessment of the safety in the most sensitive target species. The safety of the injection of one dose or two successive injections of one dose of a high antigen dose of vaccine administered intramuscularly in 3-week-old piglets was demonstrated by the:

- Absence of general reactions,
- No major and an inconsistent effect of the vaccine on rectal temperature,
- No impairment on the growth of the animals,
- A slight and acceptable level of local reactions at the injection sites.

Overall, this provided evidence of the safety profile of the vaccine in piglets of minimum age.

Another study assessed the safety of one injection of an overdose (i.e. a double dose of the vaccine containing a high dose of antigen) of Circovac vaccine administered to SPF piglets at about 3 weeks of age. The safety of the injection of a double dose of a high antigen dose of vaccine administered intramuscularly in 3-week-old piglets was demonstrated by:

- No specific effect of the vaccine on temperature,
- Absence of treatment-related general reactions,
- No impairment on the growth of the animals,
- A satisfactory level of local reactions and inflammatory reactions of muscular tissue at the injection sites.

These results reinforce the evidence of the safety profile of the vaccine in piglets of minimum age.

Field safety in 3-week old piglets

The safety of the use of Circovac in piglets has been confirmed under field conditions based upon a field trial and pharmacovigilance data gathered through the off-label use of Circovac in piglets.

A field safety study was conducted of an inactivated and adjuvanted PCV2 vaccine administered to 3 week-old piglets. The safety of the vaccine was clearly demonstrated by the study since:

- No treatment-related systemic reactions were observed,
- Temperature increase post-vaccination was moderate and very transient,
- Local reactions were rare and moderate, lasting 2 days at most,
- No impact on bodyweight gain was observed.

Overall, the satisfactory safety profile of the vaccine, already demonstrated under laboratory conditions, was confirmed under practical conditions of use.

A compilation of periodic safety update reports (PSURs) was presented that documented adverse events associated with the off-label use of Circovac in piglets under field conditions.

The safety profile of the vaccine was confirmed on a large scale under routine practice conditions and proved to be fully consistent with data gathered from laboratory studies and field trials.

As regards user safety, although the number of animals vaccinated per vaccination sequence may increase, the overall user safety is not considered affected by the addition of the sub-category of piglets in the indication. As with the existing use of the vaccine in sows, the risk from an accidental injection of the antigen can be considered as negligible. Nevertheless, as the emulsion is a standard oily formulation (it contains mineral oil and as such self-injection may be painful and dangerous), special precautions should be taken by the person administering the product to animals. Relevant warnings are provided in section 4.5 of the Summary of Product Characteristic (SPC). As regards residues, the composition of the vaccine has not changed. No MRL is required for any vaccine components and consequently in section 4.11 of the SPC "Withdrawal period", zero days is indicated.

Conclusion on the safety data

Circovac has been shown to be safe in the target animal category of piglets, under both laboratory and field conditions. Adverse events observed in piglets are reflected in the relevant sections (4.6 Adverse reactions and 4.10 Overdose) of the SPC. In light of the relatively limited experience of use of the vaccine in piglets in the field, in addition to the associated changes to the product literature, it is recommended to re-set the PSUR cycle to allow for more frequent monitoring of potential adverse events in piglets following approval of the use of the product in this subgroup of the target species.

User safety aspects related to the risk of injection of oil adjuvant to humans are adequately reflected in a warning in section 4.5 of the SPC. As regards consumer safety no risk concerning residues is identified and no change to the impact on the environment is envisaged.

Efficacy of the product in piglets

The efficacy of Circovac has been demonstrated in 3 week old piglets in laboratory and field conditions at the minimum dose.

Onset of Immunity

In order to evaluate the onset of immunity, studies have been performed on SPF piglets submitted to challenge 2 and 3 weeks after vaccination. The efficacy of the vaccine was demonstrated in 3 week old SPF piglets submitted to experimental challenge 2 weeks after vaccination by: a significant reduction of viral load and excretion of PCV2, improved growth, lower clinical scores and lower hypertrophy of lymph nodes. In addition a trend toward reduction of gross lesions was observed.

The efficacy of the vaccine was also demonstrated in SPF piglets vaccinated at 16 to 20 days of age and challenged 3 weeks after vaccination based on several parameters: a lower global clinical score, reduction of viral load and excretion (sera and faeces), lower mesenteric lymph nodes weight and a reduction of viral load and PCV2 specific lesions in mesenteric lymph nodes.

Duration of Immunity

Duration of immunity studies have been performed on conventional piglets vaccinated at 3 weeks of age and challenged with a virulent PCV2 isolate at the age of 10 and 17 weeks, respectively.

The efficacy of the vaccine was demonstrated in 3 week-old conventional piglets, in the presence of maternally derived antibodies, by reduction of both viral load in sera and faecal excretion of PCV2, as well as improved growth.

The vaccination of 3 week-old conventional piglets with 0.5 ml intramuscularly of the vaccine conferred efficient protection to vaccinated animals against a virulent PCV2 challenge performed at the age of 17 weeks, in the presence of maternally derived antibodies. This was demonstrated by significant reduction of PCV2 viral load in sera, reduction of PCV2 viral load in faeces and a tendency to lower clinical signs in vaccinates. A lower viral load in mesenteric lymph nodes and an improved growth rate were also observed in vaccinates.

Field Trials

In order to allow extrapolation of data obtained under experimental and field conditions, the representativeness of anti-PCV2 maternal antibodies titres observed in laboratory studies and in field trials was assessed and satisfactorily demonstrated by measuring anti-PCV2 maternal antibody titres in conventional piglets from the laboratory study in comparison to piglets included in field trials. The titres of serum antibodies against PCV-2 were similarly distributed without any significant difference.

Field efficacy in 3-week old piglets

The efficacy data obtained under experimental conditions were verified and supplemented by the results obtained from efficacy field trials. The effect on overall average daily weight gain (ADWG) demonstrates that vaccination with Circovac can help to control wasting and growth retardation, which are the main signs associated with PCV2 sub-clinical infection in the field, as well as protection against PCV2 associated mortality.

The results justify the beneficial use of the vaccine in piglets from 3 weeks onward, in addition to the vaccination of sows and gilts. The claim for a reduced viraemia and faecal excretion of PCV2 was also satisfactorily justified as well as the claim for 2 and at least 14 weeks onset and duration of immunity, respectively.

It was concluded that a significant reduction of PCV2 viraemia and faecal excretion was demonstrated, that a lower mesenteric lymph nodes weight, a reduction of viral load and PCV2 specific lesions in mesenteric lymph nodes had been observed in vaccinated animals as well as a tendency towards an improved growth rate. Therefore, based on this evidence, considering the associated benefit-risk assessment, and being consistent with the approach followed for sows and gilts, the following indications are considered acceptable: 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.

Various supplementary supportive field data were also provided to support these conclusions.

3. Benefit-risk assessment

3.1. Benefit assessment

The use of the vaccine to protect piglets against PCV2 infection represents an important benefit in terms of animal health. A compilation of periodic safety update reports (PSURs) was presented that documented adverse events associated with the current off-label use of Circovac in piglets under field conditions. The provision of clear guidance in the SPC by means of this variation procedure as to how the vaccine should be used in piglets reduces the risks associated with the current widespread off-label use of the product in piglets which is occurring in the absence of any relevant SPC instructions or information.

3.2. Risk assessment

Adverse events observed in piglets are adequately reflected in the relevant sections (4.6 Adverse reactions and 4.10 Overdose) of the SPC. As regards user safety, although the number of animals vaccinated per vaccination sequence may increase, the overall user safety is not considered affected by the addition of the sub-category of piglets in the indication. As with the existing use of the vaccine in sows, the risk from an accidental injection of the antigen can be considered as negligible. Nevertheless, as the emulsion is a standard oily formulation (it contains mineral oil and as such self-injection may be painful and dangerous), special precautions should be taken by the person administering the product to animals. Relevant warnings are provided in section 4.5 of the SPC. As regards residues, the composition of the vaccine has not changed. No MRL is required for any vaccine components and consequently in section 4.11 of the SPC "Withdrawal period", zero days is indicated. As regards consumer safety no risk concerning residues is identified and no change to the impact on the environment is envisaged.

3.3. Evaluation of the benefit risk balance

Circovac has been shown to be safe in the target animal category of piglets, under both laboratory and field conditions. Adverse events observed in piglets are adequately reflected in the relevant sections (4.6 Adverse reactions and 4.10 Overdose) of the SPC. In light of the relatively limited experience of use of the vaccine in piglets in the field, in addition to the associated changes to the product literature, it is recommended to re-set the PSUR cycle to allow for more frequent monitoring of potential adverse events in piglets following approval of the use of the product in this subgroup of the target species. No change to the impact on the environment is envisaged.

4. Conclusion

The CVMP concludes that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered approvable.

It is recommended to re-set the PSUR cycle for submission of further 6 monthly reports for the next two years, and then followed by yearly reports for the next two years and thereafter submission at 3 yearly intervals. This will allow for more frequent monitoring of potential adverse events in piglets following approval of the use of the product in this subgroup of the target species.