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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for a type II variation for Coliprotec F4/F18 (EMEA/V/C/004225/II/0005)

Vaccine common name: Porcine post-weaning diarrhoea vaccine (live)

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

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Introduction

The applicant submitted to the European Medicines Agency (the Agency) on 22 August 2018 an application for a type II variation for Coliprotec F4/F18. Coliprotec F4/F18 is a lyophilised vaccine for oral suspension for pigs and is intended for the active immunisation of piglets from 18 days of age against enterotoxigenic F4-positive and F18-positive *Escherichia coli* to reduce the incidence of moderate to severe post-weaning *E. coli* diarrhoea (PWD) and reduce the faecal shedding of enterotoxigenic F4-positive and F18-positive *E. coli* from infected pigs.

The proposed type II variation was to add a new therapeutic indication to Coliprotec F4/F18 for the improvement of daily weight gain in pigs at risk of *E. coli*-related disease by reviewing existing laboratory data and the provision of new field studies; thus, the application initially proposed the following therapeutic indication:

"To improve daily weight gain in pigs at risk of *E. coli* related disease".

The CVMP's revised position paper on indications for veterinary medicines, EMEA/CVMP/042/97-Rev.1-Final, provides guidance on acceptable indications for immunological veterinary medicinal products (IVMPs) and refers to "active immunisation or passive immunisation of target species", which is further elaborated to refer to "reduction of negative effects of the disease/disease complex on the performance of the target animal". The performance claim proposed by the applicant: "to improve daily weight gain in pigs" as an additional indication for the immunological veterinary medicinal product Coliprotec F4/F18 was therefore not considered acceptable.

During the procedure the applicant revised the proposed claim to: "to reduce weight loss associated with *E. coli* F4 and/or F18 related diseases". Whilst the revised claim to reduce weight loss would be in line with CVMP's revised position paper on indications for veterinary vaccines (EMEA/CVMP/042/97-Rev.1-Final) and could therefore be acceptable in principle, it was considered that sufficient data had not been provided to support the claim.

The applicant requested an oral explanation to defend their position, which was held on the 21 May 2019. The applicant proposed at that time to amend the claim to: "under field conditions, reduction in weight loss associated with *E. coli* F4 and/or F18 related diseases have been demonstrated during the pre-fattening (nursery) period for a time period of 6-7 weeks". However, the CVMP considered that the field data provided in support of a claim for a reduction in weight loss, which only covered a short period of the life of the pig, is not adequate as reduction in weight loss was not confirmed to be associated with the disease of interest.

In addition, if there was any reduction in weight loss, it should be shown to be sustained and related to the overall performance at the time of slaughter, in order to be a meaningful claim.

On 27 May 2019, a letter of withdrawal was received from the applicant.

Efficacy

Laboratory studies

In support of the proposed claim, the applicant submitted a review of existing data from two laboratory challenge studies, which were part of the initial marketing authorisation application and each included an assessment of onset and duration of immunity. These studies were not sufficiently powered to assess weight gain and daily weight gain. The reduced number of unvaccinated piglets surviving post challenge limited the meaningfulness of any analysis. The data provided were not adequate to support

the proposed claim for reduced weight loss when piglets were challenged at the current onset and duration of immunity. Reduced weight loss (based on average daily weight gain post challenge) was confirmed in only one of the onset of immunity studies and one of the duration of immunity studies. In addition, at the end of the study period there was no significant difference in body weight between vaccinated and control groups. The data presented to support the claim covered a very short period of time, which was significantly shorter than standard pig production cycles, when slaughter takes place between 6-12 months of age. The applicant argued that a claim for a reduction in weight loss during such a small time period could be considered sustained and meaningful for farrow-to-feeder enterprises (also referred as breeding herds) that typically sell their piglets as weaners at 20-30 kg live weight to the fattening enterprises. However, in the absence of any additional relevant data from the field it was not possible to confirm that any benefit was sustained. In addition, from laboratory studies, with the average daily weight gain not always statistically significantly different between treatment groups following challenge. Therefore, it was considered that insufficient laboratory data had been provided to enable the proposed claim to be accepted.

Field studies

Two new field studies were provided to support the proposed claim. The first one was specifically designed to evaluate weight gain, daily weight gain and feed conversion ratio and the second study evaluated weight gain. The primary efficacy parameter in this second study related to a different indication, which was not evaluated due to a lack of natural challenge. In both field studies, the sites were not specifically selected based on history of PWD caused by *E. coli* in order to maximise the chance of natural exposure to challenge. The data collected were analysed within the context of a potential reduction of negative effects related to the disease as a secondary efficacy parameter. It was confirmed that natural challenge was not verified during the field studies. Thus, no additional relevant field data were provided to confirm that any potential reduction in weight loss during the studies were sustained and meaningful over time and therefore the proposed claim could not be accepted.

Summary of efficacy

During the procedure the applicant revised the original proposed claim from "improve daily weight gain in pigs at risk of *E. coli* related disease" to "reduce weight loss associated with *E. coli* F4 and/or F18 related diseases". Whilst the revised claim, to reduce weight loss, could be acceptable in principle, it was considered that sufficient data were not provided to support the claim and therefore the proposed claim could not be accepted. This consideration was based on the following:

In the laboratory studies, the applicant did not provide adequate data to support the proposed claim for reduced weight loss when piglets were challenged at the current onset and duration of immunity.

Reduced weight loss (based on average daily weight gain post challenge) was confirmed in only one of the onset of immunity studies and one of the duration of immunity laboratory studies. However, the investigation carried out in these studies monitored the weight of piglets vaccinated at the minimum age with up to a 7 day window from challenge until the end of the study (maximum 46 days of age), which is a very limited observation period and not considered to be meaningful from a performance perspective. The other onset and duration laboratory study concluded that there was no statistically significant difference in the average daily weight gain; therefore, the study did not support the proposed claim for a reduction in weight loss. Overall, there was contradictory laboratory data on the effect of vaccination on weight and any effect was over a very short time period, which questioned whether any observed effect on weight loss would be meaningful and sustained over time.

Two new field studies were provided to support the proposed claim. The study sites were not specifically selected based on history of PWD caused by *E. coli* and it was confirmed that natural

challenge was not verified during field studies. Therefore, the proposed claim could not be demonstrated in the field.

The applicant argued that a claim for a reduction in weight loss during the small time period proposed could be considered sustained and meaningful for farrow-to-feeder enterprises (also referred as breeding herds) that typically sell their piglets as weaners at 20-30 kg live weight to the fattening enterprises. However, in the absence of any additional acceptable data from the field it was not possible to confirm that any benefit was sustained and related to the disease of interest.

The CVMP considered that the data submitted in this application cannot support an additional claim related to reduction of weight loss for this vaccine. It was concluded that there were insufficient efficacy data to support a meaningful claim for a reduction of weight loss associated with *E. coli* F4 and/or F18 related diseases.

Benefit-risk assessment of the proposed change

Coliprotec F4/F18 is authorised for the treatment of pigs from 18 days of age against enterotoxigenic F4-positive and F18-positive *Escherichia coli* in order to reduce the incidence of moderate to severe post-weaning *E. coli* diarrhoea (PWD) in infected pigs and reduce the faecal shedding of enterotoxigenic F4-positive and F18-positive *E. coli* from infected pigs.

1.1. Benefit assessment

Coliprotec F4/F18 is of value in the treatment of PWD due to *E. coli* which is caused primarily by ETEC, a pathotype that is characterised by production of adhesins that mediate bacterial adherence to the intestine and enterotoxins that cause diarrhoea. The types of *E. coli* associated with PWD usually have either F4 or F18 fimbrial adhesins that mediate their attachment to intestinal cells. Coliprotec F4/F18 has been shown to reduce the incidence of moderate to severe post-weaning *E. coli* diarrhoea and faecal shedding of enterotoxigenic F4-positive and F18-positive *E. coli* in pigs vaccinated from 18 days of age.

A type II variation was submitted to add a new therapeutic indication to reduce weight loss associated with *E. coli* F4 and/or F18 related diseases. No direct benefit could be demonstrated as there were insufficient efficacy data to support the proposed claim for a reduction weight loss associated with *E. coli* F4 and/or F18 related diseases.

1.2. Risk assessment

Quality, target animal safety, user safety, consumer safety and risk for the environment remain unaffected by this variation.

1.3. Evaluation of the benefit-risk balance

The applicant has not provided adequate data to support the proposed additional therapeutic indication claim to "reduce weight loss associated with *E. coli* F4 and/or F18 related diseases". There was contradictory data from laboratory studies concerning the effect of vaccination on weight loss following challenge. In addition, the data that were available related to a short timeframe which has not been shown to be meaningful or sustained. In the field studies, sites were not specifically selected based on history of disease caused by *E. coli* and in the absence of confirmed challenge, the studies did not add

any information. In view of the deficiencies in the efficacy data provided it was not possible to conclude a positive benefit-risk balance for this variation.

Overall conclusions of the evaluation

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considered that the application for variation to the terms of the marketing authorisation for Coliprotec F4/F18 is not approvable at the present time since the applicant has not sufficiently demonstrated the efficacy of the veterinary medicinal product in the therapeutic indication applied for.