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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Coliprotec F4 (EMEA/V/C/003797/0000)

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

On 18 February 2014 the applicant Prevtec Microbia GmbH submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Coliprotec F4 under Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralized procedure was agreed upon by the CVMP on 13 June 2013 as the product contains a new active substance (Article 3(2)(a) of Regulation (EC) No 726/2004). The rapporteur appointed was A.-M. Brady and the co-rapporteur was E. Augustynowicz.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

The applicant is registered as a small and medium-sized enterprise (SME) pursuant the definition set out in Commission Recommendation 2003/361/EC.

Coliprotec F4 is a lyophilized vaccine for oral use in pigs. The active substance is live non-pathogenic *Escherichia coli* strain O8:K87. Each dose contains from $1.3x10^8$ to $9x10^8$ colony forming units (cfu).

The vaccine is intended for active immunisation of pigs against F4-positive enterotoxigenic *Escherichia coli* in order to reduce the incidence, severity and duration of post-weaning *Escherichia coli* diarrhoea (PWD) in pigs and reduce the faecal shedding of F4-positive enterotoxigenic *Escherichia coli* from infected pigs to in-contact animals. The proposed target species is pigs. The proposed route of administration is for oral use.

Coliprotec F4 is presented in cardboard boxes containing 1 or 4 glass vials of 50 doses or 1 glass vial of 200 doses.

On 15 January 2015 the CVMP adopted an opinion and CVMP assessment report.

On 16 March 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Coliprotec F4.

Scientific advice

The applicant received scientific advice from the CVMP on 13 April 2012 and a follow-up scientific advice on 12 July 2012. The scientific advice pertained to quality, safety and efficacy aspects of the dossier and the follow-up to safety and efficacy.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated 17/03/2014) was provided, which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country is available. There are no outstanding issues.

Manufacturing authorisations and inspection status

Coliprotec F4 is manufactured in the European Union (EU) by CZ Veterinaria, S.A., Porriño/Pontevedra, Spain. A valid good manufacturing practice (GMP) certificate from an inspection on June 2012 has

been provided and no further inspection is required. A qualified person's statement of GMP compliance referring to *Escherichia coli* Master seed strain was provided together with confirmation that this refers to the *E. coli* strain O8:K87 strain included in Coliprotec F4.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 – Quality

Composition

Coliprotec F4 is a vaccine containing live *Escherichia coli* bacteria, strain O8:K87, from $1.3x10^8$ to $9x10^8$ cfu/dose, which is presented as a lyophilisate for reconstitution in tap water. Sucrose, monosodium glutamate and dextran 40,000 are included as excipients. The pharmaceutical form is an oral suspension.

Container

The product is presented in type I glass vials of 6 ml and 11 ml containing 50 and 200 doses respectively and are closed with chlorobutyl rubber stoppers and aluminium seals. The container and closures comply with European Pharmacopoeia (Ph. Eur.).

Development pharmaceutics

E. coli is considered to be an important cause of post-weaning diarrhoea (PWD) in piglets. Recently an increase in incidence of severe *E. coli* associated disease manifested as sudden death or severe diarrhoea has been observed worldwide. *E. coli* causing PWD mostly carry the F4 (K88) or the F18 fimbriae and a combination of several toxins. Several F4 serological variants or subtypes (ab, ac, ad) may be involved. Both for the development of disease and for the acquisition of immunity against the disease pigs must have the receptor specific to the bacterial F4 fimbriae. Around 50% of pigs carry F4 receptors on the brush borders of villous enterocytes. Based on the three serological variants of the F4 *E. coli* (ab, ac, ad), at least five pig phenotypes have been identified, being susceptible to different F4 fimbriae variants or combinations of F4 variants (ab, ac and ad). These phenotypes are either adhesive to all three variants, adhesive to ab and ac, to ab and ad, adhesive only to ad, or non-adhesive. The vaccine strain in Coliprotec F4 expresses F4 fimbriae, by far the most frequently occurring type worldwide.

Coliprotec F4 was originally developed in Canada, where it has been authorised since 2007. The *E. coli* O8:K87 strain in Coliprotec F4 expresses F4 fimbriae and it is toxin-negative. It was isolated from a healthy pig in 1999. Particular clones of the strain, of which the F4 fimbriae expression was stable, were selected. The strain is non-pathogenic for animals and humans since it is non-haemolytic and negative for the virulence associated genes and virulence factors which are associated with intestinal and extra-intestinal *E. coli* diseases.

An explanation and justification for the composition and presentation of the vaccine has been provided.

Method of manufacture

The procedure for production of the *E. coli* antigen is a conventional one for a live bacterial vaccine in a scale up system. After fermentation the bacteria are concentrated and then mixed with a stabilizer.

The vaccine is formulated at a target of $9x10^8$ cfu per dose. Final containers are aseptically filled and stoppered with vacuum closing butyl rubber stoppers that are only partially inserted. After lyophilisation, vials are fully closed under vacuum. Rubber stoppers are held firmly in place by an aluminium seal which is crimped on after vacuum stoppering.

Control of starting materials

Active substance

The organism (F4-positive, toxin-negative *E. coli* O8:K87) was isolated from faeces of a healthy pig. The origin, isolation and history are sufficiently described. The master and working seeds have been produced according to the Seed Lot System. Further clarifications for the seed materials are acceptable.

Information on the antibiotic sensitivity of the vaccine strain has been provided and it is acceptable. The vaccine strain has been considered relevant for Europe.

The only starting material used in manufacture of the vaccine that is of animal origin is the *E. coli* strain of the master seed The culture media used contain only materials of non-animal origin, and therefore the risk of TSE contamination is considered to be negligible. All the starting materials used were considered acceptable.

Excipients

Most of the starting materials of non-biological origin used in the production are Ph. Eur. compliant. Defined internal specifications and/or representative Certificates of Analysis (CoA) were provided for all starting materials. No animal derived materials apart from the *E. coli* strain are used in the manufacturing process. Since Coliprotec F4 is intended for oral use, Ph. Eur. monograph 0999 (dextran 40 for injection) does not apply and the application of internal specifications is justified.

Other excipients used are sucrose, monosodium glutamate and purified water which all comply with Ph. Eur. monographs.

Information regarding the qualitative and quantitative composition of all culture media and the stabiliser and their storage conditions is provided in the dossier.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The documentation provided for all the materials of animal origin demonstrated their compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) and Commission Directive 1999/104/EEC.

It is concluded that, the risk of transmitting transmissible spongiform encephalopathy (TSE) infectivity through the use of this vaccine is negligible.

Control tests during production

The following control tests are carried out at various stages during production of the antigen: purity, viable count by agar plate count, optical density, identification of the antigen, calculation of the concentration factor at the initial and at the final volume.

The following tests are carried out on the final bulk vaccine: purity, viable count, identification by agglutination test and fill volume.

All results met the required specifications, thereby demonstrating that the E. coli antigen is manufactured consistently.

Control tests on the finished product

The following control tests on the finished product were performed: appearance, vacuum, presentation, identity by polymerase chain reaction (PCR), identity by agglutination test, potency test by agar plate count, purity using Ph. Eur. sterility test method and residual humidity. All results met the required specifications, thereby demonstrating that the vaccine is manufactured consistently.

Stability

Stability data presented for CZ Veterinaria-produced batches are considered sufficient to allocate a 12 month shelf life for the finished product and this is based on data from 4 consecutive batches manufactured by CZ Veterinaria: 1 batch has been stored for up to 18 months and 3 batches have been stored for up to 12 months. However, the granting of a 12 month shelf life should be supported with full stability data, for up to 15 months for three consecutive batches which should be provided as soon as the data becomes available. Information on any-out-of-specification-test results should be provided as soon known. The CVMP consider this a condition to the marketing authorization.

Satisfactory data have been submitted to support the stability of reconstituted product for 4 hours after reconstitution in reverse osmosis water or tap water. The vaccine bacteria are sensitive to free chlorine that might be present in drinking water and data have been provided to demonstrate that, in such cases, it can be protected by the addition of 0.25% or 1% skimmed milk. This point is reflected in the summary of product characteristics (SPC) where addition of 0.5% of skimmed milk (5 g/l) to reconstitution water is recommended.

Overall conclusions on quality

Coliprotec F4 is a vaccine containing live *Escherichia coli* bacteria, strain O8:K87 which is presented as a lyophilisate for reconstitution in water. Sucrose, monosodium glutamate and dextran 40,000 are included as excipients. The product is presented in type I neutral glass vials closed with chlorobutyl rubber stoppers and aluminium seals complying with Ph. Eur. The manufacturing process for the vaccine is well described with sufficient details. Consistency data were provided for three batches of antigen and three batches of finished product in support of validation of the production process which is considered acceptable. Starting materials listed in a pharmacopoeia are of satisfactory quality. Production and testing of the *E. coli* master and working seeds is clearly described. Other starting materials of biological origin and starting materials of non-biological origin are acceptable. In-house preparation of media is detailed satisfactorily.

The main risks concerning TSE are considered negligible.

The in-process tests are described satisfactorily. Control tests on the finished product are described in satisfactory detail.

Data provided indicate satisfactory batch-to-batch consistency.

At present, the stability data presented for CZ Veterinaria produced batches are only sufficient to allocate a shelf life for the finished product of 12 months. The proposed shelf life of 12 months is considered acceptable based on the data available so far and providing that 15 month stability data for three consecutive batches are provided as a condition to the marketing authorization. Satisfactory data have been submitted to support the stability of reconstituted product for 4 hours after reconstitution in reverse osmosis water or tap water.

Part 3 – Safety

Safety documentation

In order to support the safety of Coliprotec F4, four laboratory studies were presented, with two out of four being in compliance with good laboratory practice (GLP) and two field studies.

Laboratory tests

Safety of the administration of one dose or an overdose

Study number 20-6-0121-12

The aim of this study was to investigate the safety of the oral administration of 1 dose of Coliprotec F4 at the maximum potency and of the oral administration of 1 overdose of Coliprotec F4 to 17–19-day-old weaned pigs. The study was carried out in Europe in compliance with GLP.

Forty two (42), 17–19-day-old weaned pigs were enrolled in this study and randomly allocated into four experimental groups: 2 groups of 12 pigs each were treated respectively with 1 dose of Coliprotec F4 at the maximum potency (≥ $9x10^8$ cfu) and 1 overdose (≥ $9x10^9$ cfu) of Coliprotec F4; 1 group of 12 pigs was kept as unvaccinated control (tap water was administered) and 1 group of 6 pigs was left untreated (sentinels). All groups included both receptor F4 (RF4)-positive and RF4-negative animals. All pigs were clinically monitored for 14 days.

Shivering was very commonly observed in vaccinated animals following vaccination and peaks of fever on isolated days. No statistically significant differences were observed between the vaccinated groups and unvaccinated groups with regard to the consistency or colour of faeces. Following vaccination body weights were significantly lower in the vaccinated group compared to the unvaccinated group.

There was no difference in the safety profile of animals with different receptor statuses.

Taking into account the variability of the results, warnings regarding increased temperature in section 4.6 of the SPC can be omitted. A significant difference in body weight was observed between the vaccinated and non-vaccinated groups and an appropriate warning was added to section 4.6 of the SPC. Shivering was commonly observed and an appropriate warning has also been added to section 4.6 of the SPC.

In conclusion, safety was supported following oral administration of 1 dose of Coliprotec F4 at the maximum potency and following oral administration of 1 overdose of Coliprotec F4 to 17-day-old weaned pigs albeit with specific warnings added to the SPC.

Prevtec Microbia Inc. 2004 - Supportive study only

Data from one additional study carried out in Canada in 2004 supported the conclusion of the safety of Coliprotec F4 in young pigs when administered orally as two doses. Results from this study could be considered only as supportive data as the study was not carried out in accordance with GLP, the batches of vaccine used were not manufactured in accordance with good manufacturing practice (GMP) and the vaccine was not administered as per recommended schedule.

Safety of the repeated administration of one dose

The safety of one repeated administration of a single dose of Coliprotec F4 was not investigated because the vaccine is intended to be administered only once. This is acceptable.

Examination of reproductive performance

The effect of the administration of Coliprotec F4 on reproductive performance was not investigated since the vaccine is not intended for breeding animals. However, in order for Coliprotec F4 to protect pigs during the first two weeks post-weaning, vaccination should take place when piglets are still in presence of the sow (before weaning). The risk for the vaccine strain to spread to sows has been considered. Data from a 14-day monitoring study of sows in the presence of vaccinated pigs showed no adverse effects in the lactating sow due to spread. This conclusion is considered acceptable. No additional warning is therefore required on the SPC.

Examination of immunological functions

No specific tests on immunological functions were carried out since the vaccine strain is non-pathogenic for the target species and it is not expected to have any effect on the immunological system of the pigs. This is acceptable.

Special requirements for live vaccines

Spread of the vaccine strain

The ability of the vaccine strain (*E. coli* O8:K87) to spread to unvaccinated target animals was investigated in the following two studies using the recommended route of administration.

Study number 20-6-0121-12

A group of 12 vaccinated pigs of 17 days of age, were vaccinated with the maximum vaccine potency ($\geq 9x10^8$ cfu) administered orally, were housed together with a group of 6 sentinels. Rectal swabs were collected daily from all animals for the duration of the study (14 days) and analysed by PCR for the presence of the vaccine strain.

Nine (9) out of 12 vaccinated pigs and 3 out of 6 sentinels resulted positive to the vaccine strain.

It can be concluded that the vaccine strain can be excreted from vaccinated animals for at least 14 days and that it readily spreads to contact sentinel animals. A warning was included in the SPC.

Study number 910479

The aim of the study was to investigate the shedding of the Coliprotec F4 vaccine strain from vaccinated pigs to unvaccinated animals under field conditions.

Rectal swabs were collected 2, 3 and 4 weeks after vaccination from 10 animals randomly selected from two field studies carried out in Germany (110474 and 110475). Thirty (30) samples were tested for the presence of F4 and O8 antigens (both expressed by the vaccine strain) by slide agglutination test and further confirmed by PCR.

No samples showed positive results.

In conclusion it can be stated that no shedding of the vaccine strain Coliprotec F4 was observed in pigs after 2, 3 and 4 weeks of vaccination under field conditions.

Dissemination in the vaccinated animal and reversion to virulence of vaccines

The potential for the vaccine strain to dissemination and/or to acquire virulence during in vivo passage was investigated in a laboratory study carried out in Canada. Although this was not conducted in accordance with GLP, the study was considered acceptable due to the use of the vaccine MS, produced to an adequate quality standard and in addition, for animal welfare reasons.

The vaccine strain was propagated through 5 in vivo passages in 5 groups of 10, 17–19-day-old pigs including RF4-positive and RF4-negative animals. The MS was administered orally at a potency of $1x10^9$ cfu per pig for the first passage, using an oesophageal tube. Three (3) days after the first oral administration faecal samples were pooled and used as the inoculum for the subsequent passage. A similar protocol was used for all subsequent passages. Necropsies were carried out on 5 pigs from the first passage group and on all pigs from subsequent passage groups. Evaluation of the ileum colonisation and of tissue tropism of the vaccine strain was performed on samples from the liver, the longissimus muscle and the mesenteric lymph nodes by PCR and cell culture.

Faeces were collected and tested daily by PCR for identification of ETEC (enterotoxigenic *Escherichia coli*)-associated virulence factors.

After each passage the vaccine strain was detected in faecal samples of some if not all vaccinated pigs for at least the first 3 days post-vaccination. Results from faecal samples also showed the presence of strains harbouring ETEC associated toxins not related to the vaccine strain, which were colonizing the intestine of the pigs in some stages of the study.

The vaccine strain was detected in the ileum of 3 pigs (2 were RF4-positive and 1 was RF4-negative). All extra-intestinal tissue samples (liver, longissimus muscle, and mesenteric lymph nodes) were negative for presence of the vaccine strain. No gross abnormalities of internal organs were observed although fluid intestinal contents were observed in some pigs. All the extra-intestinal tissue samples tested from all pigs were negative for the vaccine strain.

In conclusion the vaccine strain was propagated through five passages in pigs and did not acquire any virulence factors during these passages. In addition dissemination of the vaccine was limited to the ileum of 3 pigs.

Although the most severe infections occurred in RF4-positive animals, ETEC strains were re-isolated and some diarrhoea did occur in RF4-negative pigs. In conclusion, data showed that no different selection pressure in RF4-negative pigs that would increase the virulence of the vaccine, was found, therefore the risk of safety concerns in RF4-negative species is considered negligible.

Biological properties of the vaccine strain

Results from the above mentioned study show that the vaccine strain colonises the ileum of *E. coli* RF4-positive pigs (3 out of 5). The F4 receptor is expressed on the surface of their intestinal cells and the organism has no affinity or effect on other tissues (e.g. neurotropism) and does not colonise intestines of other animals or humans which do not have the F4-receptor.

Recombination or genomic reassortment of the strains

Results from the above mentioned study indicated that multiple in vivo passages did not enhance the ability of the vaccine strain to colonise the intestine.

The presence of more strains harbouring ETEC-associated toxins simultaneously with the vaccine strain in animals demonstrated that the vaccine strain does not acquire exogenous genetic material, as after 5 in vivo passages the vaccine strain remained genetically stable. It can be concluded that the vaccine strain is genetically stable and eliminated by animals.

Study of residues

Not required.

The active ingredient being a substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In addition the other components of the vaccine are either listed in table 1 of the annex of Commission Regulation No. 37/2010 or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this product.

The withdrawal period is set at zero days.

Interactions

No interactions studies have been carried out and a statement has been included in the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.' In addition, since the vaccine strain is a live bacterium, simultaneous use of any chemotherapeutics which are effective against *E. coli* should be avoided.

Field studies

The safety of the vaccine was investigated in 2 good clinical practice (GCP) compliant field studies carried out in Germany.

Study number 110474

A total of 697 pigs 17–25 days of age housed in a farm that reported a history of post-weaning diarrhoea were included in this study. A group of 343 pigs were vaccinated with Coliprotec F4 and a group of 354 pigs were kept unvaccinated as control group. From these two groups, 53 vaccinated pigs and 51 control animals from 17 to 25 days old were randomly selected for clinical observation. More than half (58.5%) of the pigs resulted RF4-positive by restriction fragment length polymorphism RFLP-PCR. Twenty-one (21) days post-vaccination an outbreak of *Lawsonia intracellularis* was observed in all

pens and was resolved in one week by macrolide treatment.

On the day following vaccine administration (day 1), vaccinated animals showed mean rectal temperature value of 39.7 °C, which was significantly different to the control group (39.4 °C). However, these rectal temperatures were within the normal rectal temperature range for pigs of this age and there were no differences between groups on days 2, 3 and 4. Diarrhoea, shivering and respiratory signs were observed in some pigs but no significant difference was seen between the groups. The shivering reactions observed in this study are in support of the results from the controlled laboratory study and are appropriately reflected in the SPC.

It can be concluded that the results from the field study support the conclusion that administration of the Coliprotec F4 vaccine in drinking water does not cause any safety concerns when administered to pigs of the youngest age recommended.

Study number 110475

A total of 709 pigs of 18–23 days of age were used in this field study. A group of 350 pigs were vaccinated with Coliprotec F4 and a group of 350 were left unvaccinated as controls. More than 70% of the pigs resulted RF4-positive by RFLP-PCR. The animals were monitored for adverse events for 14 days post-vaccination as part of the safety assessment.

No animal was observed with adverse events suspected to be related to vaccine administration.

Several animals developed meningitis three weeks post-vaccination, caused by *Streptococcus suis* infection, however this was not unexpected based on the farm history and was not associated with vaccine administration; both treatment groups were affected.

It can be concluded that the results from the field study support the conclusion that administration of the Coliprotec F4 vaccine in drinking water does not cause any safety concerns when administered to pigs from 18 days of age. The difference in the number of adverse events observed in the vaccinated and in the control group was not statistically significant.

Study number Prev-07 -001- Supportive study

An additional field safety study was carried out in Canada in 2007. This was not carried out in accordance with GCP and no control animals were included in the study. A total of 753 pigs of at least 19 days of age located in three different Canadian sites and geographical regions were vaccinated either by drench or via automated drinking water systems. The pigs were monitored for 14 days post-vaccination for diarrhoea, lethargy, anorexia or mortality on D1, D5 and D14 (the end of the study).

No adverse reaction was observed associated with the vaccine.

In conclusion, this field study adds support to the fact that the Coliprotec F4 vaccine does not cause any safety concerns when administered to pigs from 19 days of age. The study was not conducted to GCP and used pre-licensing batches of vaccine manufactured in Canada thus this study is considered to be of supportive value only.

User safety

A user safety risk assessment for the vaccine was provided in accordance with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006). The excipients used in the vaccine are either authorised food additives in the EU or included in the list of substances not falling within the scope of Regulation (EC) No. 470/2009.

Due to the nature of the different components of Coliprotec F4, no specific risks have been identified.

The CVMP therefore concluded that the user safety for this product is acceptable when used as recommended in the SPC.

Environmental risk assessment

An environmental risk assessment in accordance with the CVMP Note for guidance on environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95) was provided. Coliprotec F4 consists of a live avirulent non-pathogenic *E. coli* F4 strain (*E. coli* O8:K87). Only the target animal (pigs) is susceptible to this strain, as this species exclusively expresses the F4 receptor on the surface of their intestinal cells. The transmission of the strain to non-target species is theoretically possible; however colonisation of the strain in the intestine of non-target species, which is important for the development of the disease, will not occur.

The excipients do not constitute a risk to the environment.

Based on the data provided the ERA can stop at Phase I. Coliprotec F4 is not expected to pose a risk to the environment when used according to the SPC.

The following additional points were considered:

- It seems likely that other species that do not have the RF4 receptor could also develop some clinical signs after exposure to the vaccine. The point has been addressed satisfactorily in the environmental risk assessment. The risk is considered to be negligible.
- The safety for pregnant or lactating sows that might be in contact with vaccinated piglets was considered and the risk is considered to be negligible.

A Phase II assessment is not considered necessary.

Overall conclusions on the safety documentation

The safety of Coliprotec F4 was investigated in four laboratory safety studies. Two of these studies were Ph. Eur. compliant and were carried out in accordance with GLP, using finished product manufactured at CZ Veterinaria as proposed for the European market.

The administration of one dose and the administration of one repeated dose of Coliprotec F4 to pigs from 17 to 19-day-old is considered safe. A very common adverse reaction is shivering and a transient reduced weight gain may be observed in vaccinated compared to non-vaccinated pigs during the first week after vaccination.

The adverse reactions observed in this study are appropriately reflected in section 4.6 of the SPC.

The vaccine strain is excreted from vaccinated animals for at least 14 days and it readily spreads to in-contact unvaccinated pigs. An appropriate warning is included in the SPC.

Potential effect on reproductive performance were not investigated on the basis that the vaccine is not intended for breeding animals and this is considered acceptable even if pigs vaccinated before weaning would remain in contact with the sow until weaning.

The risk of safety concerns in RF4-negative species is considered negligible.

It can be concluded that potential spread of the vaccine strain and the risk of reversion to virulence, in both RF4-positive and RF4-negative pigs is considered negligible.

Residue studies are not required. The withdrawal period is set at zero days.

The user safety for this product is acceptable when used as recommended in the SPC.

In view of the ability of the vaccine strain to spread, the potential risks to users and also to sows and other animals that might be in contact with vaccinated pigs have been considered further and current warnings are deemed acceptable.

Based on the data provided the ERA can stop at Phase I. Coliprotec F4 is not expected to pose a risk to the environment when used according to the SPC. Overall it is concluded that, the vaccine is considered to be safe.

Part 4 – Efficacy

Introduction and general requirements

Coliprotec F4 is intended for the reduction of post-weaning diarrhoea (PWD) caused by F4-positive enterotoxigenic *Escherichia coli* (F4-ETEC) infection and for the active immunisation of pigs against F4-positive enterotoxigenic *Escherichia coli* in order to reduce the incidence of moderate to severe post-weaning *Escherichia coli* diarrhoea (PWD) in pigs and reduce the colonisation of the ileum and faecal shedding of F4-positive enterotoxigenic *Escherichia coli* from infected pigs.

The laboratory studies presented are compliant to the Ph. Eur. monograph 0062 on vaccines for veterinary use and Ph. Eur. monograph 5.2.7 on evaluation of efficacy of veterinary vaccines, with key efficacy and field studies conducted to GCP.

Laboratory trials

In total five studies have been conducted to establish the onset and duration of immunity on the basis of the reduction of duration, incidence and severity of PWD and on the reduction of colonization of the ileum and the shedding of F4-ETEC. Due to the non-equivalence between the Canadian site and the European site, studies that were conducted using the product manufactured in Canada could only be considered as supportive studies.

Validation of the PCR protocol used to detect *E. coli* genome was provided. The challenge strain used in the laboratory studies was an F4-ETEC strain EcL 8559 isolated in Canada. Detailed information on its origin and history were provided and the challenge strain is considered relevant for Europe.

Efficacy studies were based on the challenge model studies in which necropsy of the challenged pigs was established 3 days post-challenge when clinical signs were most apparent and although earlier than would expect PWD on farm, this was considered acceptable.

In assessing the prevalence, duration and severity of diarrhoea, only moderate to severe diarrhoea was taken into account.

Onset of immunity

Study number SRP-RA-0001

The aim of this study was to investigate the efficacy of a single dose of Coliprotec F4 administered in drinking water at minimal potency to about 17-day-old weaned pigs and evaluate the onset of immunity. This study was conducted to GCP and the vaccine was produced in Europe.

The study was designed conforming to the challenge model presented in the previous studies that were carried out in Canada. A group of 20, 17-day-old pigs, negative for faecal F4-ETEC strains by PCR, were included in the study. All pigs were RF4-positive by RFLP-PCR.

Ten (10) pigs were vaccinated with Coliprotec F4 at minimum potency ($1.3x10^8$ cfu/pig) and 10 pigs were left unvaccinated as controls. At day 7 after vaccination all pigs were challenged at the dose of $1.5x10^9$ cfu/pig. Vaccinated and control animals were housed separately following vaccination and then following challenge vaccinated and control pigs were transferred to different pens within the same room (shared the same airspace).

All pigs were clinically monitored for 10 days; assessment of diarrhoea was performed daily. Faecal samples were collected and tested for the presence of the challenge strain by PCR and culture. Blood samples and body weights were recorded on arrival, before challenge and daily from challenge until sacrifice at day 10.

Results from vaccinated pigs against results from the controls showed a significant reduction in the prevalence of moderate to severe diarrhoea, a significant reduction in excretion of the challenge strain on day 1, 2, and 3 post-challenge, a significant reduction in ileum colonisation and a significant reduction in the level of extent and severity of accumulation of fluid in the intestine. There was no difference in weight gain between vaccinated and control groups post-challenge.

The data from this study supports a reduction in the prevalence of pigs with diarrhoea however there was no difference in the duration or severity of diarrhoea. This study supports a 7-day onset of immunity in pigs from 18 days of age after vaccination with Coliprotec F4 at minimum potency on the basis of reduction in the incidence of moderate to severe PWD and a reduction in the colonisation of the ileum and faecal shedding of F4-positive enterotoxigenic *E. coli*. Circulating maternal antibodies (IgG) were present in the pigs prior to vaccination and declined during the study however there was no interference with vaccine efficacy. Antibody titres for IgM and IgA were low on day 0 and following vaccination levels increased significantly in the vaccinated group. Antibody titres were quantified in the intestines and were significantly higher in vaccinated piglets for IgA only. Nevertheless, there was a significant correlation between serology on the day of sacrifice and intestinal antibody levels for both IgM and IgA. In conclusion a 7-day onset of immunity was supported.

Study number SRP-RA-0006

This study aimed at investigating the efficacy in the reduction of PWD-associated clinical signs by a single dose of Coliprotec F4 when administered at minimal potency dose to 17-day-old target animals after a challenge at 3 days post-vaccination. This study was GCP compliant and the vaccine used was produced in Europe.

The study is designed conforming to the challenge model presented in the previous studies. A group of 40, 17–19-day-old RF4-positive pigs (confirmed by RFLP-PCR), negative for faecal F4-ETEC strains by PCR, were included in the study. Twenty (20) pigs were vaccinated, using minimum potency dose ($5.9x10^7$ cfu/pig) and 20 pigs were left unvaccinated as controls (water filtered by reverse osmosis was administered as placebo). At day 3 after vaccination all pigs were challenged at the dose of

$1.7x10^9$ cfu/pig. All pigs were clinically monitored for 8 days; assessment of diarrhoea was performed daily. Faecal samples were collected and tested for the presence of the challenge strain by PCR and culture. Body weight of all pigs was recorded on arrival, the day of challenge and at necropsy. Necropsy was performed at day 8.

Results showed that vaccinated pigs excreted less F4-ETEC challenge strain then the control pigs, however results were statistically significant only on day 5 post-challenge. The number of pigs with moderate to severe diarrhoea post-challenge was lower in the vaccinated group with respect to the control group but results were not statistically significant. After challenge results showed that average daily weight gain was higher in the vaccinated group then in the control group.

It is concluded that efficacy of a single dose of Coliprotec F4 administered in drinking water at minimum potency to pigs from 18 days of age offered limited protection following challenge 3 days post-vaccination. Fewer pigs were observed with moderate to severe diarrhoea and less excretion of the F4-ETEC challenge strain in the vaccinates compare to controls however the differences between the vaccine and control groups were not always statistically significant.

In conclusion the claimed onset of immunity at 3 days post-vaccination was not supported by this study as the full range of efficacy parameters claimed in section 4.2 of the draft SPC were not demonstrated.

Study Prevtec microbia Inc. 2007- Supportive study

The aim of this laboratory study was to evaluate the onset of immunity in terms of the efficacy of Coliprotec F4 when administered at minimal potency dose to 17-day-old pigs, to reduce mortality, clinical signs, shedding of ETEC strain colonization of the ileum, weight loss and/or lesions associated with PWD. In addition the influence of maternally derived antibodies on the efficacy of the vaccination was investigated. Although the study was not conducted to GCP, the principles were adhered to and this is considered acceptable. However, the vaccine batch used was produced in Canada and thus can only be considered a supportive study.

One group of 40 pigs, negative for faecal F4-ETEC strains by PCR, were used in the study. All pigs were also tested for the presence of IgG and IgM anti-F4 by enzyme-linked immunosorbent assay (ELISA) before vaccination. Twenty (20) pigs were vaccinated after weaning at 18 days of age, with Coliprotec F4 at minimum potency ($1x10^8$ cfu/pig). Twenty (20) pigs were kept as unvaccinated control group and given sterile water by oral drench (6 ml). Vaccinated and control pigs were housed separately. Positive F4 receptor status of the pigs was confirmed by *post mortem* cryosection and RFLP-PCR in 5 out of 20 pigs from the vaccinated group and 8 out of 20 from the control group. Pigs were challenged with an ETEC strain, at approximately $5x10^8$ cfu/pig, by oesophageal tube, on day 8 after vaccination. All pigs were clinically monitored for 11 days and assessments of diarrhoea were performed daily. Five (5) faecal samples were collected from the day of vaccination until necropsy on day 11 (3 days after challenge) and tested for the presence of the challenge strain by PCR and culture. At necropsy extent and severity of accumulation of fluid in the intestines and colonisation were evaluated. Body weight of all pigs was recorded on arrival, at challenge and at necropsy.

After challenge, from days 9 to 11, the prevalence, duration and severity of diarrhoea, the colonisation of the ileum by the challenge strain and its excretion were evaluated and comparison between groups (RF4-positive vaccinated pigs versus RF4-positive control pigs and RF4-negative vaccinated versus RF4-negative control pigs) was done.

Results showed that approximately 90% of the pigs were positive to maternally derived antibodies prior to vaccination. Considering all pigs (RF4-positive and RF4-negative) after challenge, the prevalence, the severity and the duration of diarrhoea was significantly lower in vaccinated pigs than in

the controls. Significantly fewer vaccinated pigs were colonised in the ileum by the challenge strain compared with the controls. Excretion (on days 9 and 11) of the challenge strain was significantly less in vaccinated pigs. The level, extent and severity of accumulation of fluid in the intestines were significantly lower in the vaccinated pigs compared to the controls. Moreover, the average daily weight gain was significantly higher in the vaccinated pigs than in the controls.

Regarding the comparison between RF4-positive vaccinated and RF4-positive control pigs, i.e. the target population, the proposed claims were not fully supported. The vaccinated animals showed reduced diarrhoea in terms of the prevalence, duration and severity however results were not statistically significant.

In conclusion this laboratory study in both RF4-positive and negative pigs following vaccination with Coliprotec F4 at minimal potency to 18-day-old pigs supported an onset of immunity of 7 days as demonstrated by a significant reduction in the prevalence, duration and severity of diarrhoea in vaccinate pigs compared to control. A reduction in the shedding of the ETEC strain, colonisation in the ileum and weight loss was also apparent for vaccinated pigs. Efficacy was supported in these young 18-day-old pigs in which maternally derived antibodies were present. Nevertheless, as the vaccine used was produced in Canada, the study can only be considered supportive.

Study number PREV-08-004 - Supportive study

An additional efficacy laboratory study to assess the onset of immunity was submitted with the aim to confirm result from the above mentioned efficacy study, in RF4-positive pigs at the minimum recommended age, using minimum potency vaccine. This study was conducted using a product produced in Canada, and can only be considered a supportive study.

The study was designed conforming to the challenge model presented in the previous study and although the study was not conducted to GCP, the principles were adhered to and this is considered acceptable. A group of 41, 17-day-old pigs, negative for faecal F4-ETEC strains by PCR, were included in the study. Twenty (20) pigs were vaccinated using minimum potency vaccine ($1x10^8$ cfu/pig) and 21 pigs were kept unvaccinated as controls. Eighteen (18) vaccinated pigs and 20 controls were confirmed to be RF4-positive by *post mortem* cryosection and RFLP-PCR. Results from the two RF4-negative pigs were excluded from the study. At day 8 after vaccination all pigs were challenged with a dose of $1x10^9$ cfu/pig. All pigs were clinically monitored for 11 days; an assessment of diarrhoea was performed daily. Faecal samples were collected and tested for the presence of the challenge strain by PCR and culture. Body weight of all pigs was recorded at vaccination, challenge and necropsy. Necropsy was performed at day 11.

Pigs from the vaccinated group showed a significant reduction in the excretion of the challenge strain on day 11, a significant reduction in colonisation of the ileum and a significant reduction in the level of extent and severity of accumulation of fluid in the intestine (especially in the ileum) with respect to the control group. In addition results showed a reduction in the loss of weight gain in vaccinated piglets in comparison to the controls after challenge (days 8–11).

The results confirmed the findings from the previous study. In conclusion, this laboratory study in RF4 positive pigs following vaccination with Coliprotec F4 at minimal potency to 18-day-old pigs supported an onset of immunity of 7 days as demonstrated by a significant reduction in the prevalence, duration and severity of diarrhoea in vaccinate pigs compared to control.

The presence of circulating maternal antibody in the study pigs is unknown as no samples were collected prior to vaccination.

Nevertheless, as the vaccine used was produced in Canada, the study can only be considered supportive.

Study number SRP-RA-0004- Supportive study

The aim of this study was to demonstrate the efficacy of the administration of a single dose of Coliprotec F4, at minimal potency dose, to reduce the incidence, the duration and the severity of diarrhoea and shedding of F4-ETEC strain. Although the study was not conducted to GCP, the principles were adhered to and this is considered acceptable. The study was conducted in Canada using vaccine produced in Canada, and thus this study can only be considered a supportive study.

A group of 32 RF4-positive pigs (confirmed by *post mortem* cryosection and RFLP-PCR) of 18–20 day of age, seronegative to IgG and IgM anti-F4 by ELISA and negative for faecal F4-ETEC strains by PCR, were included in the study. Sixteen (16) pigs were vaccinated with Coliprotec F4 at the minimum potency dose ($6.3x10^7$ cfu/pig) via drinking water after weaning and 16 pigs were left as unvaccinated controls. Vaccinated and control pigs were housed separately post-vaccination and commingled from challenge. At day 8 after vaccination all pigs were challenged at the dose of $1.2x10^9$ cfu/pig. Daily clinical observation was carried out for both groups of pigs, body weight was measured at day 1, 6 and 16, faecal samples were collected at day 9, 11, 13 and tested by PCR and culture for the presence of the challenge. Necropsy was performed at day 16 and samples were not collected.

There was a significant reduction in the number of vaccinated piglets compared to the controls that showed signs of diarrhoea (frequency, duration, incidence and consistency from 1–4 days post-challenge) compared with piglets which were not vaccinated. Vaccinated piglets excreted less F4-positive enterotoxigenic *E. coli* compared to the controls but only at 2 days post-challenge ($1.1x10^6$ vs. $1.2x10^7$ cfu/g). There was no difference in body weight gain following challenge.

In conclusion, this laboratory study, in RF4 positive pigs following vaccination with Coliprotec F4 at minimal potency to 18–20-day-old pigs, supported an onset of immunity of 7 days as demonstrated by a significant reduction in the number of vaccinated pigs which showed signs of diarrhoea compared to controls. Vaccinated pigs also excreted less F4 positive enterotoxigenic *E. coli* 2 days post-challenge compared to controls. Nevertheless, as the vaccine used was produced in Canada, the study can only be considered supportive.

Duration of immunity

Study number SRP-RA-0001

The aim of this study was to investigate the efficacy of a single dose of Coliprotec F4 administered in drinking water at minimal potency to about 17-day-old weaned pigs and evaluate the duration of immunity.

The study is designed conforming to the challenge model presented in the previous studies. A group of 20 pigs 18–19-day old, negative for faecal F4-positive strains by PCR, were included in this study. All pigs were RF4-positive by RFLP-PCR. Ten (10) pigs were vaccinated with the minimum potency dose ($1.3x10^8$ cfu/pig) and 10 pigs were kept unvaccinated as controls. At day 21 after vaccination all pigs were challenged at the dose of $9.5x10^8$ cfu/pig.

All pigs were clinically monitored for 24 days after vaccination; assessment of diarrhoea was performed daily. Faecal samples were collected and tested for the presence of the challenge strain by PCR and culture. Blood samples and body weights were recorded on arrival, before challenge and daily from challenge until sacrifice at day 24.

Comparison between vaccinated pigs and controls showed that vaccinated pigs had a significant reduction in the prevalence of moderate to severe diarrhoea (mainly at 3 days post-challenge), a significant reduction in excretion of the challenge strain on 1, 2, and 3 days post-challenge and a significant reduction in colonisation of the ileum. There was no significant reduction in accumulation of fluid in the intestine and no difference in weight gain between treatment groups post-challenge.

The data from this study support a reduction in the prevalence of pigs with diarrhoea however there is no difference in the severity of diarrhoea.

In conclusion this study supports a 21-day duration of immunity following vaccination of pigs from 18 to 19 days of age with a claim for a reduction in the incidence of moderate to severe post-weaning *E. coli* diarrhoea and a reduction in the colonisation of the ileum and faecal shedding of F4-positive enterotoxigenic *E. coli*.

Circulating maternal antibodies (IgG) were present in the study pigs prior to vaccination however there was no interference with vaccine efficacy. Antibody titres for IgM and IgA were low on day 0 and following vaccination levels increased significantly in the vaccinated group. Antibody titres were quantified in the intestines and were significantly higher in vaccinated piglets for both IgA and IgM but only in the jejunum. There was a significant correlation between serology (at necropsy) and intestinal antibody levels for IgA.

Field trials

Study number 110474 and study number 110475

Two field studies were conducted in the north-west of Germany with the aim to assess the efficacy of Coliprotec F4 in terms Reduction of clinical signs of post-weaning diarrhoea in piglets in Europe.

These GCP compliant studies were carried out in two different sites both declaring a history of post-weaning diarrhoea associated with *Lawsonia intracellularis* during the pre-fattening period, and meningitis associated with *Streptococcus suis.* For each study a group of 700 weaned pigs 17–18 days old, was used. Pigs from both sites confirmed a high level of RF4-positive pigs (58.5% and 70.1%) by RFLP-PCR.

In each site, 350 pigs were vaccinated with Coliprotec F4 at minimum potency (1.0 or $2.74x10^8$ cfu/pig) and 350 pigs were left unvaccinated as controls. The two groups were housed separately. Following vaccination pigs were monitored daily for general heath parameters including diarrhoea. Faecal samples were collected from a proportion of the pigs from the onset of diarrhoea to confirm the causative agent. In addition blood samples and bodyweights were recorded during the studies.

Natural challenge was confirmed on both sites. It is noted that some of the pigs resulted positive to *Lawsonia intracellularis* infection (PIA) at day 21. Due to confounding factors, evaluation of diarrhoea after day 21 was not taken into account.

From the first field study presented it can be concluded that a significant reduction in the number of pigs with moderate to severe diarrhoea following vaccination was demonstrated.

From the second field study presented it can be concluded that a reduction in the incidence of moderate to severe diarrhoea was demonstrated in vaccinated pigs.

In conclusion, on the basis of both field studies the claim for a reduction in the incidence of moderate to severe post-weaning *E. coli* diarrhoea is supported when administered Coliprotec F4 to target animals at the minimum age recommended on the SPC.

Overall conclusion on efficacy

Five laboratory efficacy studies were provided. Three of the studies used a vaccine that was manufactured in Canada and therefore the data generated could only be considered supportive data. Coliprotec F4 was used in two of GCP compliant studies which were well designed to establish the onset and duration of immunity. In addition two field efficacy studies were conducted to support the reduction in clinical signs associated with PWD.

The efficacy of Coliprotec F4 has been demonstrated in RF4-positive pigs (susceptible animals) under laboratory conditions using a challenge model which was considered acceptable.

Both routes of administration of the vaccine an oral drench and in drinking water has been demonstrated efficacious and are considered acceptable.

The efficacy parameters that were taken into account to establish both the onset of immunity and the duration of immunity were the reduction in the frequency of diarrhoea, the reduction in colonisation and shedding of F4-positive enterotoxigenic *Escherichia coli*. The impact on duration of diarrhoea was only investigated in the studies carried out using vaccine batches manufactured in Canada and these data could not be accepted.

The following indications are currently supported by the data provided:

For active immunisation of pigs of 18 days of age against F4-positive enterotoxigenic *Escherichia coli* in order to reduce the incidence of moderate and severe post-weaning *Escherichia coli* diarrhoea (PWD) in pigs and reduce the colonisation of the ileum and faecal shedding of F4-positive enterotoxigenic *Escherichia coli* from infected pigs.

Onset of immunity is set at 7 days after vaccination.

Duration of immunity is set at 21 days after vaccination.

The reduction of faecal shedding of F4-positive enterotoxigenic *E. coli* from infected pigs to in-contact animals is not currently supported by data and therefore cannot be claimed. The SPC has been revised accordingly.

It has been demonstrated that maternally derived antibodies present in the pigs did not interfere with the efficacy of the vaccine.

Part 5 – Benefit-risk assessment

Introduction

Coliprotec F4 is a live vaccine for active immunisation of pigs from 18 days of age against post-weaning diarrhoea (PWD) caused by F4-positive enterotoxigenic *Escherichia coli*. It is presented as a lyophilisate that can be reconstituted in water for administration by drench or in drinking water. Post-weaning diarrhoea (PWD) caused by F4-ETEC typically causes mild to severe watery diarrhoea between 5 to 10 days post-weaning with dehydration, loss of performance, and occasionally death. Economic losses associated with PWD are significant, due to mortality, weight loss, weight heterogeneity, treatment costs, coexisting diseases, and management of sick animals. PWD due to *E. coli* is caused primarily by strains of enterotoxigenic *E. coli* (ETEC), producing 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. The *E. coli* O8:K87 strain in Coliprotec F4 expresses F4 fimbriae and it is toxin-negative. The strain is

non-pathogenic for animals and humans since it is non-haemolytic and negative for the STa, STb, LT, VT1 (Stx1) and VT2 (Stx2) as well as for Eae, Pap, Paa, East-1, and AIDA virulence associated genes. These virulence factors are associated with intestinal and extra-intestinal *E. coli* diseases.

The dossier has been submitted in accordance with Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

In laboratory and field studies the vaccine was shown to induce active immunisation of pigs against F4-positive enterotoxigenic *Escherichia coli* in order to reduce the frequency and severity of diarrhoea (moderate to severe lesions) in a total of 733 pigs vaccinated from 18 days of age and challenged with virulent organisms 7 days later as well as to reduce colonisation and shedding of F4-positive enterotoxigenic *E. coli*. The product was shown to have an onset of immunity of 1 week (7 days) post-vaccination with duration of immunity of 3 weeks (21 days).

Additional benefits

Vaccination of young pigs against post-weaning diarrhoea caused by *E. coli* may lead to a reduction in the use of therapeutic antibiotics.

The vaccine is administered by drench or in drinking water and is therefore easy to apply.

The vaccine reduces the shedding of F4-positive enterotoxigenic *Escherichia coli* and may therefore reduce the field contamination by this organism.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of Coliprotec F4 is well described and specifications set will ensure that product of consistent quality will be produced provided that conditions are fulfilled.

For the target animal:

The product is generally well tolerated in the target animal.

The safety of Coliprotec F4 was adequately assessed in the minimum age group recommended for vaccination. A very common adverse reaction observed was shivering of the pigs after vaccination and a transient reduced weight gain during the first week after vaccination. The adverse reactions observed in this study are appropriately reflected in the SPC.

The vaccine strain is a non-pathogenic strain, lacking the genes coding for virulence factors, however has the ability to spread to in-contact unvaccinated pigs and other species. However the risk to develop clinical diseases for species exposed to the vaccine strain is considered negligible.

The vaccine organism is sensitive to free chlorine that might be present in drinking water and data have been provided to demonstrate that, in such cases, it can be protected by the addition of 0.25% or 1% skimmed milk concentrations as a stabilizer. It is recommended to use a dose of 0.5% (5 g/l).

For the user:

The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

For the consumer:

A residue study is not required. The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, consumer, and the environment and to provide advice on how to prevent or reduce these risks. A condition to the marketing authorization was considered necessary regarding provision of 15 month stability data for the three consecutive batches on stability testing.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The vaccine contains a live non-pathogenic *Escherichia coli* strain O8:K87. It is intended to induce active immunisation of pigs against F4-positive enterotoxigenic *Escherichia coli* in order to reduce the incidence of moderate to severe post-weaning *Escherichia coli* diarrhoea and reduce the colonisation of the ileum and faecal shedding of F4-positive enterotoxigenic *Escherichia coli*.

The formulation and manufacture of Coliprotec F4 is well described and in general specifications set would ensure that product of consistent quality will be produced. Based on the stability data provided, a 12 month shelf life is acceptable considering the provision of 15 month stability data for the three consecutive batches on stability testing which is set as a condition to the marketing authorization.

Coliprotec F4 is well tolerated by the target animals and presents an acceptable risk for users, consumers and the environment when used as recommended and appropriate warnings have been included in the SPC.

The withdrawal period is set at zero days.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with sufficiently clear and complete product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP concluded that the quality, safety and efficacy of Coliprotec F4 were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Coliprotec F4.