EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the scientific discussion for the approval of **Porcilis Porcoli Diluvac Forte** (as published in June 2011). For information on post-authorisation changes please refer to module 8 (Steps taken after authorisation).

1. Summary of the dossier

Porcilis Porcoli Diluvac Forte is an inactivated multivalent subunit vaccine. It provides passive immunisation of piglets by active immunisation of sows/gilts. It is indicated to reduce mortality and clinical signs such as diarrhoea due to neonatal enterotoxicosis during the first days of life, caused by those *E. coli* strains which express the fimbrial adhesins F4ab (K88ab), F4ac (K88ac), F5 (K99) or F6 (987P). The fimbrial adhesins F4ab, F4ac, F5, and F6 are responsible for the adhesion and the virulence of *E. coli* strains, which cause neonatal enterotoxicosis in piglets. These immunogens are incorporated in an adjuvant in order to enhance a prolonged stimulation of immunity. Mild, transient clinical reactions (fever, lethargy) may occur in the first 24 hours after vaccination. Swelling and redness at the injection site may occasionally last for at least 14 days.

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2. Quality assessment

Composition

Names of ingredients	Quantity per dose of 2 ml	Function	Reference to standards
Active and other substances			
F4ab (K88ab) fimbrial adhesin	≥ 9.0 $\log_2$ Ab titre[1]	Induction of immunity	Internal reference immunogen
F4ac(K88ac) fimbrial adhesin	≥ 5.4 $\log_2$ Ab titre	Induction of immunity	Internal reference immunogen
F5 (K99) fimbrial adhesin	≥ 6.8 $\log_2$ Ab titre	Induction of immunity	Internal reference immunogen
F6 (987P) fimbrial adhesin	≥ 7.1 $\log_2$ Ab titre	Induction of immunity	Internal reference immunogen
LT toxoid	≥ 6.8 $\log_2$ Ab titre	Induction of immunity	Internal reference antigen
dl-alpha-tocopherol acetate	150 mg	Adjuvant	Ph. Eur.
KCl	-	Isotonicity	Ph. Eur.
KH_2PO_4	-	Buffer	Ph. Eur.
NaCl	-	Isotonicity	Ph. Eur.
Na_2HPO_4	-	Buffer	Ph. Eur.
Polysorbate 80	-	Emulsifier	Ph. Eur.
Simethicone	-	Anti-foam	USP
Water for injection	-	Diluent	Ph. Eur.

Justification for the choice of the active substances and the adjuvant as well as clarification as to the functions of the other ingredients of the vaccine was given.

Container

The vaccine is presented in a cardboard box with 1 PET or glass (hydrolytic Type I) vial of 20, 50 ml or 100 ml with a halogenobutyl rubber stopper and a coded aluminium cap. The methods of preparation, sterilisation and closure were described

Development Pharmaceutics

The production method and processes are described, specified and validated in an appropriate manner. A concentrate of each adhesin of the vaccine is produced from inactivated (heating and formalin) bacterial cultures after filtration, washing and concentration procedures. The heat-labile enterotoxin (LT) toxoid is purified and detoxified (heating and formalin). Filling of the antigens with adjuvant concentrate (dl-alpha-tocopherol acetate), closing and sealing are achieved by automated procedures.

Production is in accordance with the principles and guidelines of Good Manufacturing Practice laid down in Commission Directive 91/412/EEC. Batch to batch consistency of production was supported by data from 3 batches. The antigen concentrates of the vaccine are prepared from the following production strains: *E. coli* K12JA 221-pPab-2, *E. coli* K12JA 221-pPac-2, *E. coli* K12JA 221-pPLT-1, *E. coli* K12JA 221-pOK99-2 and *E. coli* 09: K103, 987P-5. The quality of these strains was described in monographs supplied by the applicant.

The construction processes of the plasmids, the junction sequences and sequences of the inserted genes, the estimation of the plasmid copies, the constructional and segregational stability and residual

[1]Mean antibody titre (Ab) obtained after vaccination of mice with a 1/20 sow dose.

transforming activity and the preparation of the master- and working seed lots for vaccine production were described and specified. The specifications of the master- and working-seed lots were given.

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

Information and satisfactory reassurance were provided for Porcilis Porcoli Diluvac Forte.

Control tests during production

According to the flow chart of the method of preparation and quality control procedure regarding the F4ab, F4ac, F5 and F6 adhesins and the LT, the following in process tests are described and specified (for the LT, a Vero cell test is also done): sterility test of medium, purity test of inoculum, purity test of culture, inactivation test, determination of immunogen/LT toxic activity, sterility of immunogen concentrate.

The validation study showed that the inactivation test for the F4ab vaccine strain is sufficiently sensitive in the presence of low levels of chlorocresol with a detection limit of 1 colony forming unit (CFU) per ml.

The reference antigens, used in the ELISA assay, for quantification of the antigenic masses of all antigens, were specified.

Control tests on the finished product

The relevant monograph is Ph. Eur. monograph for neonatal piglet colibacillosis inactivated vaccine, number **01/2008:0962**. Appropriate testing is carried out to ensure sterility, safety and potency of the vaccine. Checks on endotoxin content and acidity are also carried out.

As an in-process control, the antigen content of the bulk antigens is determined by antigenic mass ELISAs. As a finished product control, the antibody responses of vaccinated mice against F4ab, F4ac, F5, F6 and LT are measured by antibody ELISAs. The two specific tests ensure that each batch of the vaccine contains the substances indicated.

After production of the bulk antigens of the vaccine, the amount of the antigens is determined using antigenic mass ELISAs. Based on these determinations, a fixed amount of the antigens is used to formulate the finished product. Therefore, no minimum and maximum potent batches exist for the vaccine. In potency testing of this type of vaccine, the observed variations in results are mainly due to the potency test itself and not to differences in the intrinsic properties of the batches of the vaccine.

Data were, however, provided to demonstrate that batches of the vaccine, with lower amounts of the antigens, are detected by the batch potency test. It was considered that the batch potency test with the current release requirements, combined with the antigenic masses determination of the bulk antigens to calculate the necessary quantity to obtain the fixed amounts of antigens to formulate the finished product of the vaccine, provided a sufficient guarantee for vaccine batches of constant quality within the specifications.

A batch of the vaccine was used for setting the potency release requirements and used to demonstrate protection in a vaccination/challenge experiment in pigs. The batch passed the set release requirements and was demonstrated to be protective. The average responses of the batches used for setting the release requirements, which were not tested in vaccination-challenge experiments, were comparable to those of the above mentioned batch. Batch to batch consistency of production is supported by data from three representative batches of the vaccine.

Stability

Stability of the finished product

Data on the stability of the finished product in glass and PET vials were presented. Both container types were used from the beginning of the tests. Stability data generated with the 20 ml presentation (glass and PET) can be considered to represent a worst case The endotoxin content of two batches of the vaccine was also tested. The data on the endotoxin presence and persistence in the vaccine showed a slow reduction of the endotoxin content.

A shelf life of 12 months was extended to 24 months via subsequent variation of the authorisation.

In use Stability

As the vaccines will be used mainly on farms with more than 25 pigs, the rubber stopper of the vial will mainly be pierced once. If the stopper were to be penetrated every time a dose of the vaccine is extracted, considered to be an unlikely event, the maximum number of penetrations would be ten as in this case the smallest presentation would normally be used. If this affected the self sealing ability of the stopper, there would be no negative effect on the vaccine as the in-use shelf-life is 3 hours. The stoppers used met the Ph. Eur. requirements for self-sealing after
10 penetrations.

Environmental risk assessment for products containing or consisting of genetically modified organisms

As neither vaccine contains a GMO capable of replicating in the environment, this section is not applicable.

Overall conclusion on quality

There are sufficient details on the production process to ensure consistency of production. Overall the quality of the vaccine was considered satisfactory with the appropriate follow-up measures in place.

3. Safety assessment

Laboratory tests

Safety of the administration of one dose

Commercial healthy pigs of 19 weeks of age were intramuscularly vaccinated with one dose of vaccine in the neck. The pigs used originated from a herd free from neonatal *E. coli* enterotoxicosis for ten years and were not vaccinated. The pigs would, therefore, have no, or low, antibody titres. The pigs were observed for 14 days after vaccination. Post-mortem investigation was carried out on all pigs at 27 days after vaccination; as well as histological examination. It was considered acceptable that the pigs were not of the target category (pregnant) as data were presented from studies where a repeated dose and an overdose had been administered to pregnant pigs.

Twenty per cent of pigs were less active, but these pigs were normal on day 2 after vaccination. The other pigs showed no signs of disease. An increase of 1.0 – 2.0°C (mean: 1.5°C) in body temperature was observed which resolved on day 2 after vaccination. No local reactions were seen or palpated at the injection site. At post-mortem examination 60% of pigs showed small granulomas at the injection site: 0.05 – 1.4 cm^3 (mean: 0.56 cm^3). No vaccine remnants were observed.

Safety of an administration of an overdose

Healthy commercial pregnant pigs (from a farm with no history of porcine neonatal *E. coli* enterotoxicosis or associated vaccination) were vaccinated contemporaneously by the intramuscular route with one dose of the vaccine on the right side and with one dose of the vaccine on the left side of the neck. At the time of vaccination, most of the pigs had antibodies against the adhesins of the vaccine. The pigs were observed for 14 days after vaccination. Fifty three per cent of pigs were less active, but 47 per cent of pigs became normal on day 2 after vaccination. The last pig became normal on day 3 after vaccination. The other pigs showed no signs of disease.

It was noted that fifty three per cent of sows had antibodies at the beginning of the study and of these 6 per cent failed to respond against F4ab, F5 and the LT; another 6 per cent against F5 and 12 per cent against LT antigen. A comparison of the groups of pigs with and without antibodies showed no differences in the observed local reactions, general impression of the animals or the reproduction data. There were differences in the body temperature of the pigs in both groups after overdose and single repeated dose but these differences were not significant. There was no apparent correlation between the pre-vaccination antibody titres and the body temperature increase. No significant difference in the increase of the body temperature was found between the group of pigs with and without pre-vaccination antibodies.

Safety of the repeated administration of a dose

Four weeks after the start of the investigation on the safety of an overdose, each of the pigs concerned received an intramuscular booster vaccination, with one dose of the vaccine in the neck.

Minor local reactions were seen in a small number of animals. A small number of animals also had an increase of 0.1 – 1.8°C (mean: 0.9°C) in body temperature which disappeared by 28 hours after vaccination. One percent of animals had a diffuse local reaction of ca. 5 cm in diameter at the injection site which had disappeared on day 6 after vaccination. Two per cent of pigs had a local reaction of 0.5-1.0 cm which disappeared by day 2 after vaccination. The other pigs did not show any local reactions at the injection site.

Examination of reproductive performance

The pigs used in the investigation of safety of the booster dose were also used to study the safety of the vaccine on the reproductive performance of pregnant pigs. The pigs were observed until after farrowing. The reproduction results of the sows and gilts in the study were considered to be within the normal range on the farm concerned. No evidence was found for a negative influence of the vaccine on the gestation neither of vaccinated pigs nor on the quantity or quality of their progeny.

Examination of immunological functions

No evidence is available in the published literature which suggests that the use of a vaccine of this type could have a negative influence on the immune response of either the sows or their progeny. In addition, given the nature of the vaccine, such influence is very unlikely. The Committee agreed that the absence of further data on the examination of immunological functions in the dossier was acceptable.

Interactions

No information on the safety and efficacy from the concurrent use of Porcilis Porcoli Diluvac Forte with any other was presented and therefore an appropriate warning is included in SPC.

Residue assessment

The adjuvant and excipients used are either allowed substances for which no MRLs are required or are considered as not falling within the scope of the MRL Regulation. As a result of the composition of the vaccine no specific residue studies were considered necessary. A withdrawal period of zero days was considered acceptable.

The CVMP (Committee for Medicinal Products for Veterinary Use) agreed that, since withdrawal times are in principle based on residue depletion, it was not appropriate to require such withdrawal times in the context of local tissue reactions.

Field studies

Two field trials were carried out with a standard formulation of the vaccine:

Trial 1

A reduced food intake and/or less activity was observed in 10 – 15% of the vaccinated pigs on the first day after the primary/booster vaccination compared with 4 – 6% in the placebo pigs. These signs of disease had disappeared within 24 hours. Some loss of activity in some of the vaccinated/placebo treated pigs was observed during the second week after the vaccination/placebo treatment. An increase in body temperature (mean: 0.8ºC) was observed
5 hours after primary vaccination compared with 0.3ºC in the placebo group. Five hours after booster vaccination an increase of body temperature (mean: 0.6ºC) was observed compared with 0.4ºC in the placebo group. Within 24 – 48 hours of the vaccination/placebo treatment, the increase of body temperature had resolved. A mild reaction (redness or non-painful swelling
< 5 cm in diameter) at the injection site after primary/booster vaccination was observed in 5 – 9% of the pigs, compared with 2% in the placebo groups. The reactions persisted for 1 – 2 weeks after vaccination/placebo treatment.

Trial 2

Groups of breeding sows per farm were selected from commercial farms. The selection of the pigs was primarily governed by availability. The objective was to vaccinate and observe one group of pigs per farm. In order to achieve this, the vaccination 'window' was extended from 14-28 days to 14-65 days before the expected date of farrowing. No other selection criteria were applied. Some 50 per cent of pigs were vaccinated with Porcilis Porcoli Diluvac Forte and the remainder with Porcilis Porcoli (a mineral oil adjuvanted vaccine for which the marketing authorisation has subsequently been withdrawn). Each pig received one dose of vaccine by the recommended route of administration at 2 – 10 weeks (mean: 5 weeks) before farrowing. The pigs were observed at 1 and 6 – 8 hours after vaccination/placebo treatment and daily for 5 days thereafter, for signs of disease. Reactions at the injection sites were observed on day 1, 3 and 5 after vaccination. Body temperature was measured rectally at 6 – 8 hours after vaccination. Most systemic reactions were mild, with the highest incidence at 6 – 8 hours after vaccination. The incidence was significantly different between the two vaccination groups (Porcilis Porcoli Diluvac Forte: 5.1% and Porcilis Porcoli: 0.6%). In the majority of these cases the signs of disease had disappeared by 24 hours, but 1% (Porcilis Porcoli Diluvac Forte) and 0.6% (Porcilis Porcoli) persisted for another day. The latter percentages were not significantly different.

User safety

There is a risk associated with self-injection and text to this effect has been included in the SPC and package leaflet.

Environmental Risk Assessment

The CVMP considered that a phase I environmental risk assessment level was justified and that a phase II level assessment was not required. The risk for the environment is considered negligible.

Overall conclusions on safety

The data contained in the dossier demonstrated that the safety of the product was in accordance with the requirements in force at the time of submission.

4. Efficacy assessment

One laboratory challenge study (according to Ph. Eur. monograph 0962) was carried out on piglets from pigs vaccinated with a standard formulation of the vaccine.

Design:
- unvaccinated pregnant pigs from a commercial farm without a history of porcine neonatal *E. coli* enterotoxicosis were vaccinated intramuscularly: a primary dose of vaccine 6 – 8 weeks before farrowing followed by a booster dose of vaccine 4 weeks later. Other pregnant pigs from the same farm acted as controls.
- piglets from the vaccinated and unvaccinated pigs were challenged within 12 hours after birth, orally, with virulent challenge strains of *E. coli* containing adhesins which are in the vaccine. Mortality and diarrhoea scores were recorded during the 7 days after challenge.
- Serological investigations were carried out in vaccinated and unvaccinated pigs.

The pigs used in this trial were vaccinated with the product on a commercial farm. The challenge experiment was performed according to principles of GLP. All vaccinated pigs were gilts.

Regarding all adhesin groups, most of the piglets from the control pigs either died or suffered from severe diarrhoea during the observation period after challenge. The majority of the piglets from the vaccinated pigs survived and showed only, mostly mild, diarrhoea for 1 day. A clear reduction of mortality/diarrhoea was found in the piglets from the vaccinated pigs compared with those from the unvaccinated pigs.

No colostrum was taken from 18% of vaccinated sows and gilts. These samples have to be taken just before farrowing and some of the pigs involved in this study gave birth during the night. They were not observed for a few hours and the piglets concerned had already suckled colostrum.

Only a limited number of serum samples were taken from gilts just before farrowing. The serum sampling was carried out just before farrowing, but was stopped in case the sows and gilts became too agitated. As the main objective of this study was the challenge, sufficient pigs had to be available for this purpose. Moreover, since piglets are protected by suckling colostrum, the colostrum samples are the best samples for establishing a relation between the antibodies and the protective effects, although a correlation exists between antibody titres in serum and colostrum.

The data from this study are the only efficacy data obtained from vaccination/challenge experiments and they do not always strictly meet the requirements of the Ph. Eur. monograph concerned. Whilst

the vaccine does not meet all the requirements of the Ph. Eur. 'to the letter', it fulfils the main objective of the Ph. Eur. and this was considered to be acceptable.

Gilts were vaccinated according to the recommended vaccination schedule. Piglets having more than 1 day of diarrhoea were considered to have severe diarrhoea. The results are given in the following summary, which demonstrates that the vaccine meets the most important requirements of the Ph. Eur.:

- in the control groups more than 40% of the piglets died, indicating that the challenge was sufficiently severe
- in the groups of piglets from vaccinated sows and pigs far less than the required 13.3% died or had severe diarrhoea. This demonstrated the ability of the product to reduce death and severe diarrhoea after challenge with enterotoxic *E. coli*.

The 'no clinical signs' criterion of the Ph. Eur. for control animals was met for all challenges except the F4ac challenge. In the last case, however, as for all other challenge experiments, a highly significant difference was found between the vaccinated and the control group with respect to mortality and severe diarrhoea (Fisher exact test: p=0.000 for the difference between death and death and severe diarrhoea).

In 50 % of challenges, the 'mild diarrhoea' criterion of the Ph. Eur. for the vaccinated group was not met. The total percentages for the F5 and F6 adhesins were 29% (0% mortality and 29% mild diarrhoea) and 33.3% (3.7% mortality and 29.6% mild diarrhoea) respectively. This means that both challenges would have met the Ph. Eur. requirement if the distribution between the number of dead piglets and piglets with mild diarrhoea had been less favourable i.e. when more piglets had died.

For all challenges a highly significant difference in death, death and severe diarrhoea, and number of piglets without any signs of disease, was observed between the piglets from the vaccinated and from the control sows (p=0.000 Fisher exact test). A reduction, of at least tenfold, of death and severe diarrhoea is seen in the vaccinated groups compared with the control groups.

Although the challenges carried out with both F4 fimbrial adhesin variants containing *E. coli* strains may be considered "double" (adhesin F4 and LT) challenges, this was considered to be justified as the Ph. Eur. monograph 0962 specifies, regarding the challenge in the potency test: 'Carry out the test with a challenge strain against which the vaccine is intended to protect: If a single strain with all necessary antigens is not available, repeat the test using different challenge strains'. LT is predominantly secreted by *E. coli* strains which express F4 adhesins or, a combination of F4 and F6 adhesins. Non-fimbriated *E. coli* strains which secrete LT are not pathogenic as they will not be able to adhere to enterocytes in the small intestines. It is not, therefore, possible to perform a challenge experiment in which only such a strain is used. Hence, F4ab, LT+/F4ac, LT+ challenge strains were used and a separate LT challenge was not carried out.

In contrast to whole bacteria vaccines, the requirement for a different vaccine strain and challenge strain cannot be applied to subunit vaccines which contain a defined protein as the active component. The active component in a subunit vaccine is, by definition, homologous to the protein present on field strains to which efficacy is claimed. Moreover, since only a defined active component is present in the vaccine, protection can only be mediated by an immune response induced by this component. The recombinant vaccine strains used for the production of the F4ab, F4ac and F5 adhesins and the LT are different from the *E. coli* challenge strains used. For the F6 adhesin, the production strain and the challenge strain were homologous. However, the vaccination/challenge experiment concerned maintains its validity, considering the potential risk that the observed protection is not mediated by the immune response induced by the F6 immunogen i.e. the claim made for the vaccine.

In the literature a series of Ph. Eur. compliant challenge experiments in which the efficacy of colostrum antibodies against the F6 immunogen were assessed, both by challenge with a homologous and a heterologous *E. coli* strain. In these experiments, the F6 adhesin proteins were isolated from the same F6 adhesin strain as used by the applicant. The results show that a F6 adhesin vaccine made from the same strain as used by the applicant significantly reduced death and diarrhoea after challenge with the homologous strain as well as with the heterologous *E. coli* strain. The seroresponse data demonstrated that the protection induced by F6 adhesin vaccines is mediated by antibodies against the F6 adhesin, but not by antibodies against the O-antigen of the vaccine strain.

The protective properties of the antibodies against LT of *E. coli* were, however, not sufficiently supported by specifically related data. In the literature, LT is generally considered as a virulence factor of *E. coli* but this was not considered to be scientifically or specifically fully proven, but more considered to be circumstantial evidence. Only one of the presented references was considered to be partly supportive of the protective value of the *E. coli* LT. This reference does, however, only mention vaccination with single LT and challenges with a homologue (serotype O8: F4ab: H19) and heterologous (O149: F4ac) enterotoxic *E. coli* containing F4 adhesin and LT. No reference was submitted which included vaccination with single LT and single LT challenge, although valid reasons for this were given.

The challenge which was carried out in piglets from vaccinated sows/gilts according to the Ph. Eur. was not considered to fully demonstrate the efficacy of the vaccine. The Ph. Eur. monograph 0962 is only intended to describe and prescribe the minimum potency of a vaccine. The challenge mentioned in the Ph. Eur. regarding this type of vaccine relates to the potency/immunogenicity and not to the (full) efficacy.

The vaccination/challenge experiment to determine the minimal LT antitoxin level of the vaccine to be protective was an experiment with no single LT vaccination and no single LT challenge.

Further to the above, the application for Porcilis Porcoli Diluvac Forte was an extension of the existing Community marketing authorization for Porcilis Porcoli. No relevant other public literature was available for the application for Porcilis Porcoli. In the assessment of the application of the latter, LT was not accepted as a protective active component of the vaccine. It was, therefore, concluded that LT could not be considered as a protective substance of the vaccine and no reference to LT could be made in the indication.

A serological investigation was performed in vaccinated pregnant sows and gilts. In the first pregnancy, they were vaccinated at approximately 2 and 6 weeks before farrowing. In their next pregnancy, 38 % of them were re-vaccinated at 2 weeks and 56 % of pigs at 7 weeks before farrowing. Serotitres were determined just before the primary injection of the basic vaccination and just before the re-vaccination in the second pregnancy. During farrowing after the first and second pregnancies serotitres in the colostrum were also determined.

On the basis of the data obtained, pregnant pigs which receive a basic vaccination, and a single re-vaccination (at either 2 or 7 weeks before farrowing) in the next pregnancy, will induce a protective antibody response against the adhesins of the vaccines

Field trials

As part of a safety field trial ELISA, antibody titres against the immunogens of the vaccine were determined in sera (at primary and booster vaccination) and colostra (at farrowing) of vaccinated and placebo treated sows and gilts. The overall statistical analysis of the trial suggested that the levels of antibodies were similar to those in the laboratory/challenge trial. From the re-analysis of the data from the field trial it was concluded that vaccination with the product resulted in average antibody levels in

the colostrum of the vaccinated pigs which are significantly higher than the antibody levels in the colostrum of control pigs. Antibody levels in the colostra of the vaccinated pigs are not significantly different from antibody levels in the colostrum of the protected gilts in the vaccination-challenge experiment. A highly significant difference between the percentage of vaccinated and control pigs having antibody titres in the colostrum was found. They are equal or higher than the lowest colostrum antibody titres for which protection was demonstrated in the vaccination-challenge experiment.

The lack of sero-response of some of the vaccinated pigs is in line with the general experience that there are no vaccines known which are capable of inducing a (protective) immune response in 100% of vaccinated animals. The indication in the SPC is drafted to reflect this.

Overall conclusion on efficacy for Porcilis Porcoli Diluvac Forte

Investigation of the efficacy of the vaccine was done by one laboratory test and a field trial. The protective properties of the antibodies against LT of *E. coli* were not sufficiently supported. LT could not, therefore, be considered to be a protective substance and no reference to it is made in the indication. The vaccination schedule was considered to be appropriate. Apart from the LT component of the vaccine, the efficacy part of the dossier was considered to be acceptable.

5. Benefit risk assessment for Porcilis Porcoli Diluvac Forte

Introduction

Porcilis Porcoli Diluvac Forte is a multivalent subunit vaccine, indicated for the passive immunisation of piglets by active immunisation of sows/gilts to reduce mortality and clinical signs such as diarrhoea due to neonatal enterotoxicosis during the first days of life, caused by those *E.coli* strains which express the fimbrial adhesins F4ab (K88ab), F4ac (K88ac), F5 (K99) or F6 (987P).

Benefit assessment

Direct therapeutic benefits:

Porcilis Porcoli Diluvac forte is used to immunise piglets to reduce death and clinical signs of enterotoxicosis caused by *E. coli* bacteria during the first days of their life. The vaccine provides passive immunity to the progeny against *E. coli* fimbrial adhesins F4ab, F4ac, F5 and F6. The fimbrial adhesins F4ab, F4ac, F5, and F6 are responsible for the virulence of *E. coli* strains, which cause neonatal enterotoxicosis in piglets. Neonatal piglets derive passive immunity via ingestion of colostrum from vaccinated sows/gilts.

Risk assessment

With Porcilis Porcoli Diluvac Forte a mean transient increase in body temperature of about 1°C, in some pigs up to 3°C, may occur in the first 24 hours after vaccination. Reduced feed intake and listlessness may occur in approximately 10% of the animals on the day of vaccination, but returns to normal within 1-3 days. A transient swelling and redness at the injection site may be observed in approximately 5% of the animals. The diameter of the swelling is in general below 5 cm, but in some cases a larger swelling may occur. Swelling and redness at the injection site may occasionally last for at least 14 days.

Risk management or mitigation measures

Appropriate warnings have been placed in the SPC to warn of the potential risks to the target animal and to the user.

Evaluation of the benefit risk balance

The vaccine was administered to pregnant gilts and sows which were then observed until after farrowing. The reproduction results of the sows and gilts were considered to be within the normal range on the farm concerned. There was no evidence of any negative effects on the gestation neither of the pigs nor on the quantity or quality of their progeny.

Safety data from field trials were presented. The observed systemic side-effects (increase in body temperature, reduced feed intake and listlessness) after vaccination with the product were transient as all affected pigs returned to normal within 1-3 days of vaccination. Local reactions occurred in approximately 5% of pigs; consisting mainly of transient swelling and redness at the injection site. In general, the size of the swelling was below 5 cm, but in some cases larger swellings were observed. These local reactions could occasionally last for up to 14 days. The potential systemic side effects and local reactions were considered acceptable and suitable text, warning users about these potential undesirable effects, was included in the SPC.

A phase I environmental risk assessment was presented and it was concluded from this that the overall risk to the environment was negligible. Based on this, a Phase II environmental risk assessment was not considered to be necessary.

The safety part of the dossier was, therefore, considered to be acceptable.

Efficacy data from one vaccination/challenge study conducted in pregnant gilts were presented. Regarding all adhesin groups, a clear reduction of mortality/diarrhoea was found in the piglets from the vaccinated, compared with those from the unvaccinated, gilts. Although the data did not always strictly meet the requirements of the Ph. Eur. monograph concerned, they were considered acceptable as they fulfilled the main objective of the monograph. As the protective properties of the antibodies against LT of *E. coli* were not sufficiently supported by specifically related data, it was concluded that no reference to LT could be made in the indication for the vaccine.

The vaccination schedule, of an injection preferably administered 6-8 weeks before the expected date of farrowing followed by a second injection 4 weeks later, and then revaccination during the second half of subsequent pregnancies preferably 2-4 weeks before the expected date of farrowing, was considered to be valid. Data from two field trials were presented but these only represented antibody titres. The lack of sero-response of some of the vaccinated pigs was considered to be in line with the general experience that there are no vaccines known which are capable of inducing a (protective) immune response in 100% of vaccinated animals. The indication in the SPC was drafted to reflect this.

Apart from the LT component of the vaccine, the efficacy part of the dossier was considered to be acceptable. Based on the original and complementary data of the dossier the CVMP concluded that and the benefit-risk balance was favorable.

Conclusion on the benefit risk balance

Whilst the claimed efficacy of the LT toxoid has not been proven, no other major issues regarding the efficacy were called into question, and the Committee concluded that the claims were adequately supported by the data presented.

The product has been shown to have a positive benefit risk balance for use in pigs. There are sufficient details of the production processes to ensure consistency of production. Overall the quality of the vaccine was considered satisfactory.

The safety studies conducted by the applicant support the safety of the product.

Overall the benefits of this vaccine outweigh the risks and therefore the balance is considered positive.

Based on the original and complementary data of the dossier the CVMP concluded that the benefit-risk balance was favourable.