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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for ReproCyc ParvoFLEX (EMEA/V/C/004858/0000)

Common name: Porcine parvovirosis vaccine (inactivated)

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

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Introduction

The applicant Boehringer Ingelheim Vetmedica GmbH submitted on 28 February 2018 an application for a marketing authorisation to the European Medicines Agency (the Agency) for ReproCyc ParvoFLEX, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (product developed by means of a biotechnological process).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 June 2017 as ReproCyc ParvoFLEX has been developed by recombinant DNA technology.

ReproCyc ParvoFLEX is an immunological product for *Suidae* (inactivated porcine parvovirus viral vaccine) containing porcine parvovirus (PPV) 27a viral protein 2 (VP2) as the active substance and a carbomer adjuvant. The active substance of ReproCyc ParvoFLEX is not included in any other veterinary product approved in the EU and is therefore considered a new active substance.

The indication for treatment is:
For active immunisation of gilts and sows from the age of 5 months to protect progeny against transplacental infection caused by porcine parvovirus.

The target species is pigs. The product is administered by intramuscular injection (intramuscular use). The dose is 2 ml per animal.

ReproCyc ParvoFLEX is a suspension for injection and is presented in high density polyethylene multi-dose bottles (closed with rubber stoppers and aluminium caps) containing 20 ml (10 doses), 100 ml (50 doses) and 200 ml (100 doses). The bottles are then presented in outer packs containing 1 or 12 bottles.

The rapporteur appointed is Frida Hasslung Wikström and the co-rapporteur is Ellen-Margrethe Vestergaard.

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

On 21 February 2019, the CVMP adopted an opinion and CVMP assessment report.

On 26 April 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for ReproCyc ParvoFLEX.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system, which is

accepted. The Applicant will also submit an updated version after approval.

Manufacturing authorisations and inspection status

Manufacture of the final product takes place in the USA. The site has a valid manufacturing authorisation issued by the United States Department of Agriculture. Good Manufacturing Practice (GMP) certification confirming the date of the last inspection and showing that the site is authorised for the manufacture of such veterinary dosage forms has been provided and is acceptable.

Secondary packaging may take place inside or outside the EEA. The sites hold valid manufacturing authorisations in compliance with legislation.

A GMP declaration for the active substance(s) manufacturing site (Boehringer Ingelheim Vetmedica Inc. St. Joseph, Missouri, USA) was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release into the EU (Boehringer Ingelheim Vetmedica GmbH, Binger Strasse, Germany), which has taken into consideration the valid GMP certificate available for the active substance manufacturing site issued by a German competent authority (Kreisverwaltung Mainz-Bingen), following inspection.

Overall conclusions on administrative particulars

The GMP status of the active substance and of the finished product manufacturing site (Boehringer Ingelheim Vetmedica Inc. St. Joseph, Missouri, USA) has been satisfactorily established, and is in line with legal requirements.

Part 2 – Quality

Qualitative and quantitative particulars

ReproCyc ParvoFLEX is a subunit veterinary vaccine presented as a suspension for injection consisting of PPV 27a viral protein 2 (VP2) as active substance, and a carbomer adjuvant. Other ingredients are sodium chloride and water for injections. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC. The vaccine is administered intramuscularly to pigs using a volume of 2 ml per dose.

Containers and closure

The vaccine is filled into pre-sterilised high-density polyethylene (HDPE) multi-dose bottles according to the requirements of Ph. Eur. 3.2.2. The HDPE containers are sterilised by irradiation in accordance with Ph. Eur. 5.1.1, before filling. The containers are closed with rubber stoppers in accordance with Ph. Eur. 3.2.9, and aluminium seals. The stoppers are sterilised by autoclaving for ≥ 30 min at ≥ 121 °C.

The containers are considered acceptable and meet relevant Ph. Eur. requirements.

Product development

ReproCyc ParvoFLEX is a subunit vaccine consisting of PPV 27a VP2 protein. The PPV 27a strain was originally isolated in Germany in 2001; it is representative of isolates currently circulating in Europe. Porcine parvovirus 1 (PPV1) strains were recently classified by the International Committee on Taxonomy of Viruses as Ungulate protoparvovirus 1. The PPV 27a VP2 protein is produced in an expression system that requires insect host cells. The carbomer adjuvant is known to have immunity-enhancing characteristics without any adverse effects. The product development section includes brief information about the choice of vaccine strain, production cell line, production medium, adjuvant and manufacturing process. The recombinant PPV 27a VP2 antigen has been characterised in line with applicable regulatory requirements.

Description of the manufacturing method

The production process is based on the seed-lot-system described in the Ph. Eur. monograph 0062. The manufacture and filling of the finished vaccine are carried out according to principles of GMP, thereby establishing a process that is reproducible and appropriate for the manufacturing of the vaccine. Flow charts detailing the steps taken during the preparation of the finished product were submitted. Details of the production steps involved in the growth of the vaccine strain were provided.

The antigen PPV VP2 is a novel subunit antigen.

The finished product manufacturing process includes blending of the bulk vaccine followed by aseptic filling of the bottles, capping and then storage of finished product.

The manufacturing process and control is in general acceptably described. The results from the validation runs met all specifications. Results of the inactivation kinetics study were in line with the requirements of Ph. Eur. 0062, section 2.3.2 and the "Guideline on requirements for the production and control of immunological veterinary medicinal products" (EMA/CVMP/IWP/206555/2010 Rev.1) and are considered acceptable.

The validation of the blending and filling steps was in general acceptably performed. The claimed range of the batch size has been revised, and is found acceptable.

Production and control of starting materials

Starting materials listed in pharmacopoeias

All starting materials of non-biological origin are listed, and certificates of analysis have been provided which conform to the current relevant specifications in the Ph. Eur.

Starting materials, not listed in pharmacopoeias, of biological origin

Master and working seed virus

A detailed description of the genetic engineering of the PPV 27a VP2 master seed virus (MSV) is given. The methods and materials used during production of the MSV are stated. The TSE/BSE risk of the MSV is considered negligible. The tests performed on the MSV are in accordance with Ph. Eur. 0062.

A general description of the working seed virus (WSV) is provided, including the manufacturing method and the tests performed on each batch. Testing summaries are provided for WSV batch used in the validation studies and one other batch.

Master and working cell seed

The master cell stock (MCS) has been described acceptably. The source and history are described with sufficient detail. The working cell stock (WCS) has been described with sufficient detail. Two other WCS are described in the master batch protocols. Sufficient information regarding testing of the two WCS has been provided.

The tests performed on WCS and MSC are well described and are performed in accordance with Ph. Eur. 5.2.4 and EMA/CVMP/IWP/206555/2010-Rev.1 (Annex 2).

Testing was performed for extraneous agents from porcine and bovine origin. Some tests were not performed, however, acceptable justification for those has been provided.

The WCS cultivated up to the highest cell passage allowed for antigen production was tested in accordance with Ph. Eur. 5.2.4.

Other starting materials of biological origin

Serum-free medium is used during the production of PPV VP2. The full composition of the medium is not available, due to proprietary rights. This is considered acceptable. The TSE risk is considered negligible.

An acceptable example of a certificate of analysis (CoA) is provided for the medium.

TSE declaration

A valid TSE declaration is provided, stating compliance to Ph. Eur. 5.2.8 and EMA/410/01, rev 3. It has been determined that the materials used during production do not contain any material from TSE-relevant animal species. Materials of animal origin (non-TSE-relevant animal species) used in the production of this product are of no or minimum risk for transmission of animal spongiform encephalopathy agents.

Control tests during the manufacturing process

The PPV VP2 antigen specification was provided and includes analysis of identity, potency (antigen titre), sterility, mycoplasma and relevant production-related parameters. The analytical data and results provided are considered acceptable.

Method descriptions and validations are provided for all methods included in the antigen specification, both as brief summaries and appended reports. In general, the descriptions and validations are sufficiently detailed.

Control tests on the finished product

The finished product specification includes appearance, pH, identification, potency (relative comparison to a reference vaccine), sterility and carbomer content.

In combination with the testing of the antigen bulk, the selection of tested attributes in the finished product specification covers all relevant aspects. The descriptions and validations of the testing methods for the finished product are acceptable.

Potency assay on the finished product:

The finished product potency assay is validated as per VICH GL1 and GL2. The values of the test samples are compared to a reference vaccine to determine a relative potency (RP).

The potency method is in general considered acceptable. Different standards are used compared to the bulk antigen. The use of the reference standard batch and the positive control batch is adequately justified.

Batch-to-batch consistency

To demonstrate consistent quality of the final product, manufacturer´s batch protocols of an adequate number of consecutively produced batches are provided. The batch results submitted fulfil the proposed specifications for finished product.

Stability

Active ingredient

An adequate number of batches of PPV VP2 antigen has been included in a long-term and short-term stability study. The data confirm that the antigen is stable for up to 27 months at 5±3 °C and for up to 7 days at room temperature, with respect to potency. Sterility at end of shelf life has been verified.

Finished product

An adequate number of consecutive batches of ReproCyc ParvoFLEX, manufactured according to Part 2.B, were included in a real-time stability study. The batches were produced from different bulk antigen lots. All final product batches were stored at 5±3 °C in the packaging materials described in Part 2.A. The data indicate no stability issues during the studied period of 27 months. Some variability was seen in the potency assay, but this is attributable to method variation. The proposed shelf life can be accepted.

In-use stability

An in-use shelf life of 8 hours after first opening of the finished product when stored at room temperature has been justified for ReproCyc ParvoFLEX. Sterility and pH have been evaluated in accordance with EMA/CVMP/IWP/250147/2008. The proposed in-use shelf life of 8 hours is considered acceptable.

In-use stability – associated use with ReproCyc PRRS EU

The SPC states that ReproCyc ParvoFLEX can be mixed with ReproCyc PRRS EU which is a live-attenuated vaccine against PRRS where the applicant is the MAH. The adjuvant content is not expected to be affected by the mixing with the lyophilised vaccine. Potency of the PPV component after mixing was not tested. This is acceptable for inactivated vaccines when the proposed shelf life after mixing is less than 10 hours (EMA/CVMP/IWP/250147/2008). Taking into account that the PPV component is manufactured in a liquid form, mixing with ReproCyc PRRS EU is not expected to have an impact on the PPV potency. The potency data provided for ReproCyc PRRS EU support the proposed in-use shelf life of 8 hours after mixing.

Overall conclusions on quality

The ReproCyc ParvoFLEX vaccine is a suspension for injection consisting of the PPV 27a viral protein 2 as active substance and a carbomer adjuvant. The product is presented in multi-dose HDPE bottles containing 20 ml (10 doses), 100 ml (50 doses) and 200 ml (100 doses). The vaccine is administered intramuscularly to pigs using a 2 ml dose.

ReproCyc ParvoFLEX is based on the recombinant protein PPV 27a VP2.

Information on the development, manufacture, starting materials and control of the active substance and the finished product has in general been presented in a satisfactory manner.

Characterisation of the recombinant PPV 27a VP2 antigen has been performed with respect to primary structure, protein purity by SDS-PAGE and western blot, and total protein content.

Batch results submitted from adequate number of consecutively produced batches demonstrated acceptable batch-to-batch consistency. All results fulfilled the proposed specifications for finished product.

Data from adequate number of batches of PPV VP2 antigen confirm that the antigen is stable for up to 27 months at 5±3 °C, with respect to potency and sterility. Data from stability studies for the finished product indicate no stability issues during the studied period of 27 months (at 5±3 °C).

Part 3 – Safety

Introduction and general requirements

ReproCyc ParvoFLEX contains the PPV structural protein VP2 originating from a recent European parvovirus strain (strain PPV 27a) as active substance, and carbomer as adjuvant. The vaccine is administered intramuscularly using a 2 ml dose.

Safety was demonstrated in compliance with Art 12(3) of Directive 2001/82/EC, EMA/CVMP/IWP/206555/2010, Ph. Eur. 5.2.6, the specific Ph. Eur. monograph 0965 and VICH GL44.

Safety documentation

Six studies were conducted to investigate the safety of the product including four laboratory studies and two field trials. The vaccine was administered by the intramuscular route, as recommended using vaccine batches containing the maximum release potency of 10 RP or 10 µg of antigen per 2 ml dose in laboratory studies. In the multicentre field trial, routine vaccine batches were used, with intermediate release potency (4.6—5.0 RP/2 ml dose).

In addition, four laboratory efficacy studies with additional safety monitoring were submitted. Safety was also evaluated for the associated use of ReproCyc ParvoFLEX mixed with the PRRS vaccine ReproCyc PRRS EU.

Study title
Repeated Dose GLP Safety Study of a Killed Porcine Parvovirus Subunit Vaccine when Administered to Breeding-Age Gilts and Boars
Single Dose GLP Safety Study of a Killed Porcine Parvovirus Vaccine when Administered to Breeding-Age Gilts
Safety of a Porcine Parvovirus (PPV) subunit vaccine in lactating sows
Target Animal Safety Study to evaluate the Safety of a Repeated lx Dose of Porcine Parvovirus Vaccine in pregnant Sows
Multisite Field Safety and Efficacy trial of a Porcine Parvovirus (PPV) killed vaccine in Spain
Field safety and efficacy study in breeding sows/gilts for associated vaccination of ReproCyc PRRS EU with a porcine parvovirus (PPV) subunit vaccine in Spain
Minimum Immunizing Dose for a Killed *Erysipelothrix Rhusiopathiae* and Porcine Parvovirus (PPV) Subunit Vaccine when Administered to Gilts Pre-Breeding and Challenged with PPV at 40 Days of Gestation
Onset of immunity for a Porcine Parvovirus (PPV) subunit Vaccine
Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and challenged with PPV at 6 months and 12 months after vaccination
Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and six months after the primary course following challenge with PPV at six months post re-vaccination

Laboratory tests

Four laboratory studies investigating the safety of ReproCyc ParvoFLEX in accordance with the requirements of Ph. Eur. monograph 0965 were presented. In addition, four combined safety and efficacy laboratory studies were included. All safety laboratory studies were randomised, blinded and placebo-controlled, conducted according to Good Laboratory Practice (GLP), and the efficacy laboratory studies according to Good Clinical Practice (GCP).

The safety evaluation in the laboratory safety studies related to the safety of the administration of one dose, the repeated administration of one dose, and administration during pregnancy and lactation. Studies were performed in the target animal species (pigs) and in the most sensitive categories (young gilts, pregnant animals) using the recommended route of administration (intramuscular injection).

In all studies, local reactions, systemic reactions and rectal temperatures were monitored to assess safety. For the safety evaluation, pyrexia was defined as an increase in body temperature from baseline of ≥ 1.5 °C. In addition, to assess reproductive safety in pregnant animals and during lactation, the reproductive performance of sows and general health of the offspring were monitored.

Safety of the administration of one dose

Evaluation of safety of the administration of a single dose of vaccine was included in studies where animals were given repeated administrations and is presented in section safety of the repeated administration of one dose.

Safety of the administration of an overdose

No overdose studies are required for inactivated vaccines.

Safety of the repeated administration of one dose

Three laboratory studies were performed to evaluate the safety of the repeated administration of one dose of the vaccine corresponding to the basic vaccination schedule, i.e. two doses with a two-week interval.

One study evaluated the safety of the repeated administration of one dose of the vaccine corresponding to the basic vaccination schedule and revaccination where one dose of the vaccine was administered on three occasions with a three- or two-week interval.

Safety during lactation and the associated use by mixing with another vaccine (ReproCyc PRRS EU) was evaluated in one of the studies and safety during pregnancy was evaluated in another study.

Repeated Dose GLP Safety Study of a Killed Porcine Parvovirus Subunit Vaccine when Administered to Breeding-Age Gilts and Boars

Eight seronegative gilts, 5—6 months old were vaccinated twice with a two-week interval and 4 gilts served as controls. In addition, four boars were included in the treatment group and two boars in the control group.

No treatment-related local or systemic adverse reactions were observed after vaccination. Pyrexia was not seen in any animal. The highest individual increase in body temperature compared to base line was 0.5 °C and the maximal individual body temperature was 40.1 °C on D17. None of the animals was pyrexic on any of the monitoring days.

Single Dose GLP Safety Study of a Killed Porcine Parvovirus Vaccine when Administered to Breeding-Age Gilts

Ten seronegative gilts, 4 months old were vaccinated twice with a two-week interval and four gilts served as controls.

Local adverse reactions at the injection site were recorded as redness in two gilts after both 1st and 2nd administration and as swelling in six gilts after the 2nd administration in the vaccine group, and as redness in one gilt in the control group after the 2nd administration. Swellings were mild (<5 mm) and transient and resolved spontaneously within five days. Redness resolved spontaneously within two days.

No systemic adverse reactions or abnormal clinical observations associated with the treatment were seen. The control group showed a significantly higher mean rectal temperature than the vaccine group on three occasions (D5, D13, and D24); however, none of the animals were pyrexic on any of the monitoring days. The highest individual increase in body temperature compared to base line for a vaccinated animal was 1.0 °C and the maximal individual body temperature was 40.5 °C.

Safety of a Porcine Parvovirus (PPV) subunit vaccine in lactating sows

Nine seronegative lactating sows, 7—8 months old, were vaccinated twice with a two-week interval with ReproCyc ParvoFLEX, 9 were administered a mix of ReproCyc ParvoFLEX and a PRRS vaccine (ReproCyc PRRS EU), and 5 gilts served as control. The first administration took place two days after the last sow had farrowed.

Six of the sows administered ReproCyc ParvoFLEX developed mild injection site reactions with redness (6 sows) at the injection site and swelling (2 sows); 1 sow in the group administered the mixed vaccines showed mild redness, and 3 sows in the control group showed mild injection site reactions (3 redness, 1 swelling). The maximum size of a swelling was 1 cm. All injection site reactions resolved spontaneously within 24 hours.

No other treatment related adverse reactions or abnormal clinical observations were recorded. No animal was pyrexic during the course of the study. The highest individual increase in body temperature was 1.2 °C and the maximal individual body temperature was 40.3 °C. The percentage of weaned piglets and the mean body weight, weight gain or average daily weight gain in piglets was comparable between groups.

Target Animal Safety Study to evaluate the Safety of a Repeated lx Dose of Porcine Parvovirus Vaccine, in pregnant Sows

Ten pregnant seronegative gilts, 7—8 months old, were administered one dose of ReproCyc ParvoFLEX on gestation days 43, 64 and 78. In a second phase of the study, 10 additional pregnant seronegative gilts, 8 months old, were administrated one dose on gestation days 71, 92 and 106. Five gilts served as controls during the first phase of the study.

Mild redness at the injection site was noted in one vaccinated gilt 1 hour after the first vaccination. The redness resolved spontaneously within 24 hours. No other treatment related local or systemic adverse reactions were observed. No animal was pyrexic during the course of the study. The maximal individual body temperature was 39.0 °C. With regard to parameters in piglets (body weight, total weight gain, average daily weight gain and percentage of piglets with clinical findings), results were comparable between groups.

Based on the results from these four laboratory safety studies, safety of one dose and the repeated administration of a single dose of ReproCyc ParvoFLEX corresponding to the basic vaccination schedule and revaccination is considered acceptable. The studies support the safety of the use of ReproCyc ParvoFLEX during all phases of pregnancy and lactation, as well as the safety of the associated use of ReproCyc ParvoFLEX and ReproCyc PRRS EU during pregnancy and lactation.

Examination of reproductive performance

Two laboratory studies (already summarised above) were provided to demonstrate safety of the use of ReproCyc ParvoFLEX during lactation, and pregnancy, respectively.

From the first study in lactating sows, data have been provided showing comparable safety results in the vaccinated group and the control group with regard to the number of weaned piglets. The average daily weight gain in piglets was also numerically similar in both groups, implying no negative effects from the vaccination on the milk yield.

In the second study, sows were vaccinated during pregnancy (between gestation days 43 and 106). The treatment group was numerically comparable to the control group with regard to the total number of piglets, and the number of live, healthy, weak, stillborn, mummified or crushed piglets. Piglet health and body weight gain during the suckling period were also comparable between groups.

In one of the field studies, reproductive performance was evaluated by comparison of return to oestrus, abortion rate and number of piglets per litter at farrowing and at weaning between the test group administered with ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU and the comparator group administered with an authorised vaccine against PPV (Parvoseng). Sows and gilts were vaccinated according to the recommended schedule with a basic vaccination of two administrations of a single dose with a three-week interval followed by a revaccination by a single dose administered six months later. Sows were vaccinated before mating or during lactation. Results were comparable between the groups for all safety parameters evaluated. Safety for the proposed basic vaccination schedule and revaccination with administration of one dose six months after the

basic vaccination was shown to be acceptable.

In a supportive field study, reproductive performance was evaluated by comparison of the proportion of live piglets at weaning, return to oestrus, abortion rate, number of piglets per litter at farrowing and average daily weight gain of piglets between the test group administered with ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU and the comparator group administered with ReproCyc PRRS EU. All breeding age animals were vaccinated irrespective to the reproductive stage once with a single dose. Results for all reproductive parameters were comparable between groups.

In four laboratory challenge studies, animals were vaccinated before pregnancy, and results relating to reproductive parameters were evaluated as part of the assessment of efficacy and evaluated in part 4. Overall, there were no treatment related adverse reactions with respect to reproductive performance identified in these studies.

The data presented support the safety of ReproCyc ParvoFLEX used alone or in association (mixed) with ReproCyc PRRS EU in lactating and pregnant sows.

Examination of immunological functions

No studies have been conducted to investigate the effects of the product on immunological functions. This is acceptable on the basis that the vaccine is inactivated and therefore not expected to have adverse effects on immunological functions. The vaccine contains inactivated subunit antigens only thus no replication in immune cells is possible. Other detrimental effects on the immune system are not anticipated.

User safety

The applicant has presented a user safety risk assessment, which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006.

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection. The active substance is an inactivated protein and is not infectious. The excipients including adjuvants are commonly used in other vaccines and do not pose a risk for the user.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

No study of residues has been performed and this is acceptable since no substance requiring a maximum residue limit (MRL) is included.

MRLs

The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009.

The excipients, including adjuvants, listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The antibiotic used in the manufacturing process is present at low residual levels in the finished product and therefore is not considered to constitute a risk to the consumer.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

Data have been presented to support the associated use by mixing of ReproCyc ParvoFLEX with the PRRS vaccine ReproCyc PRRS EU. One laboratory safety study was performed. Monitoring of safety of the associated use after mixing of ReproCyc ParvoFLEX with ReproCyc PRRS EU was also performed in two laboratory challenge studies and under field conditions in two field studies.

In all studies, mild local adverse reactions were observed in 4% (redness) and 7% (swelling) of evaluated animals after administration of the mixed vaccines. The maximum size of a swelling was 10.5 cm. In all cases, local signs were transient and resolved spontaneously within two days (redness) or three days (swelling). Overall, local reactions were comparable to or milder than reactions seen after vaccination with ReproCyc ParvoFLEX alone.

There were no systemic adverse reactions attributable to vaccination in either of the studies investigating safety of the associated use. Body temperatures were comparable between groups administered with the associated vaccines or ReproCyc ParvoFLEX alone.

Data on the associated use of ReproCyc ParvoFLEX with products other than ReproCyc PRRS EU have not been provided.

In conclusion, acceptable safety has been demonstrated for the associated use of ReproCyc ParvoFLEX and ReproCyc PRRS EU in gilts and sows; also, during pregnancy and lactation.

Field studies

One multicentre, randomised, blinded, active-controlled study was conducted at three sites in Spain. In the first phase of the study, basic vaccination with two administrations of ReproCyc ParvoFLEX at an intermediate antigen dose with a 3-week interval as proposed for basic vaccination was evaluated. In a second phase, revaccination with a single administration after six months was evaluated.

ReproCyc ParvoFLEX was administered to two groups of animals, either as only treatment or as associated by mixing with ReproCyc PRRS EU. Pigs in the control group were vaccinated with a comparator PPV vaccine (Parvoseng) currently registered in the EU.

Sporadic cases of local reactions were seen (redness and swelling). All local reactions resolved spontaneously within three days, and all cases of redness within one day. The maximum size of a swelling was 4.2 cm.

No treatment-related systemic adverse reactions or abnormal clinical signs were demonstrated in these animals. Rectal temperatures differed between groups during the basic vaccination phase, with higher mean rectal temperatures in the comparator group at three occasions compared to the test groups. The elevations in rectal temperature resolved spontaneously within two days in all cases. Reproductive parameters (return to oestrus, abortion rate, number of piglets per litter at farrowing and at weaning) were comparable between the test groups and the comparator group

during both phases of the study.

The results of the field trial indicated that safety of ReproCyc ParvoFLEX is acceptable when used as recommended in the SPC with a basic vaccination consisting of two doses given with a three-week interval and revaccination with one dose six months after basic vaccination.

In addition, one supportive field study was provided to investigate the safety and efficacy of ReproCyc ParvoFLEX when used in association (mixed) with ReproCyc PRRS EU under field conditions. This study was a single-site, randomised, blinded, active-controlled study including 594 sows and gilts divided into two groups of 297 animals each. Groups received a mix of ReproCyc ParvoFLEX and ReproCyc PRRS EU, or ReproCyc PRRS EU alone.

Clinical observations were recorded for 14 days in all sows and gilts. Rectal temperature and injection sites were evaluated in sample animals (30 animals from the PPV+PRRS group and 30 from the PRRS only group) for 7 and 14 days after vaccination, respectively.

The only registered injection site reaction was mild swelling, seen in three animals in the group administered with the mixed vaccines. The swelling in all cases resolved without any treatment within 1—4 days and the maximum size recorded was 2.5 cm. One animal per group was pyrexic with an elevation of rectal temperature >1.5°C above baseline (maximum individual increase from baseline was 1.6°C). The elevation in the rectal temperature in both cases resolved without any treatment and did not last longer than two consecutive days.

In conclusion, groups appeared comparable regarding all the evaluated safety parameters.

Environmental risk assessment

An environmental risk assessment has been conducted in accordance with the CVMP Note EMEA/CVMP/074/95. The components (all) and/or excreted metabolites of the product are not toxic to the environment. The environmental exposure is negligible. Based on the data provided, the ERA can stop at Phase I. ReproCyc ParvoFLEX is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Four laboratory studies to investigate the safety of one dose and the repeated administration of one dose have been presented. In the studies, sows of the minimum recommended age were administered vaccine of the maximum titre as recommended in the SPC.

Mild local adverse reactions consisting of transient redness and swelling (up to 4 cm) were demonstrated in more than 1 but less than 10 animals in 100 animals treated. The reactions resolved spontaneously within two to five days.

An elevation in the body temperature after vaccination was commonly seen which resolved spontaneously within 24 to 48 hours. No systemic adverse reactions attributable to vaccination or other abnormal clinical results were demonstrated.

Safety data from field studies and combined safety and efficacy laboratory studies supported the conclusion that safety of administration of one dose and the repeated administration of one dose is acceptable.

Safety of vaccination with respect to reproductive performance was investigated in laboratory

safety studies and in field trials. The product was found to be safe when used in pregnant animals (all three trimesters), and also in lactating animals.

Safety has been evaluated for the associated use of ReproCyc ParvoFLEX when mixed with another vaccine, ReproCyc PRRS EU. Data from laboratory as well as field studies has been presented and results show mild local reactions indicating that safety of administration of the association was acceptable and comparable to that seen for ReproCyc ParvoFLEX when administered alone. Data with respect to safety of administration of the associated vaccines during pregnancy has also been presented.

A user safety risk assessment was made in accordance with the guideline EMEA/CVMP/IWP/54533/2006. No hazard has been identified and the risk to the user can be considered very low.

All substances included in the composition of the vaccine are listed in Annex 1 of Commission Regulation (EU) 37/2010 with a 'no MRL required' classification or in the list of substances considered as not falling within the scope of Council Regulation (EEC) No 470/2009. Consequently, a withdrawal period of zero days can be established.

ReproCyc ParvoFLEX is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Introduction and general requirements

ReproCyc ParvoFLEX suspension for injection is a subunit vaccine for pigs consisting of Porcine parvovirus 1 (PPV1; recently classified by the International Committee on Taxonomy of Viruses as Ungulate protoparvovirus 1) VP2 protein and carbomer as adjuvant.

The vaccine is intended for active immunisation of gilts and sows from the age of 5 months to protect progeny against transplacental infection caused by porcine parvovirus.

The basic vaccination schedule consists of the administration by the intramuscular route of two doses of 2 ml, separated by an interval of 3 weeks, with the second dose administered at least 3 weeks prior to mating. Re-vaccination is proposed to be performed as one intramuscular injection of one dose every 6 months in a whole herd programme. The onset of immunity is at the beginning of the gestation period and duration of immunity is 6 months.

Justification of the choice of vaccine strain

In general, PPV isolates globally are considered antigenically similar. The strains circulating at present in Europe predominantly belong to clusters C and D. ReproCyc ParvoFLEX contains the VP2 protein from the PPV 27a strain that belongs to cluster C and was originally isolated in Germany in 2001. It is considered to be representative of isolates currently circulating in Europe. Published data thus indicate that the PPV 27a strain could be suitable to induce immunity both against newly emerged and older PPV isolates.

The use of VP2 as antigen is relevant as this is one of the two capsid proteins confirmed to induce neutralising antibodies. The VP2 protein is known to be conserved among PPV strains, which may suggest that sufficient cross-protection can be obtained. Published data indicate that the PPV-27a strain antiserum is capable of neutralising several commonly occurring parvovirus strains from

different clusters.

Protection afforded by ReproCyc ParvoFLEX was demonstrated in laboratory challenge studies against a heterologous European PPV strain belonging to cluster D and against recent strains isolated during field studies in Europe.

The efficacy was investigated in accordance with Annex I of EC Directive 2001/82/EC as amended and in accordance with:

- Ph. Eur. monograph 5.2.7 Evaluation of efficacy of veterinary vaccines and immunosera
- Ph. Eur. monograph 0965 Porcine parvovirosis vaccine (inactivated)

Challenge model

No studies were conducted to establish a challenge model. Ph. Eur. monograph 0965 sets out the challenge parameters for PPV vaccines, and these requirements were applied. The challenge isolate used in all but one laboratory study was the PPV Strain 401/09 (198669), originally isolated in 2001 from Northern Germany. Based on comparison of the complete VP1 sequence, this EU challenge strain belongs to a separate phylogenetic cluster than the PPV 27a, used to construct the MSV, and therefore the heterologous nature of the EU challenge strain was confirmed.

The laboratory challenge was done consistently in all studies: each gilt received a dose of the challenge virus of 6.0 $\log_{10}$ $TCID_{50}$ in 6 ml; 2ml/each nostril intranasally and 2 ml intramuscularly. The challenge model was therefore considered appropriate for the demonstration of efficacy of vaccination in laboratory conditions.

Efficacy parameters and tests

The primary efficacy parameter investigated in the laboratory efficacy studies as stated in Ph. Eur. monograph 0965 was the number of piglets from vaccinated gilts protected from infection, as determined by the presence of virus in the foetuses detected by polymerase chain reaction (PCR). The vaccine complies with the test if no less than 80% of the piglets are protected against infection. Foetal condition, viraemia in gilts/sows and serology to PPV were included as secondary endpoints. In the field study, the proportion of mummified piglets per litter was used as the primary efficacy parameter whereas seroconversion to PPV and other reproductive parameters (return to oestrus rate; abortion rate; number and proportion of healthy live, weak and stillborn piglets per litter in the treatment groups; number and proportion of piglets per litter at weaning) were used as secondary parameters.

Efficacy documentation

Five studies were conducted to investigate the efficacy of the product and included four laboratory challenge studies and one field trial. The laboratory studies investigating the immunogenicity of the vaccine were conducted in accordance with the requirements of the Ph. Eur. monograph 0965 and in accordance with the principles of GCP. The studies were randomised, blinded and placebo-controlled. Vaccine batches containing the minimum antigen content of 1.0 µg/2 ml of the PPV VP2 antigen were administered by the recommended intramuscular route. The field study was randomised, blinded and positive-controlled using batches of an intermediate potency.

Study title
Minimum Immunizing Dose for a Killed *Erysipelothrix Rhusiopathiae* and Porcine Parvovirus (PPV) Subunit Vaccine when Administered to Gilts Pre-Breeding and Challenged with PPV at 40 Days of Gestation
Onset of immunity for a Porcine Parvovirus (PPV) subunit Vaccine
Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and challenged with PPV at 6 months and 12 months after vaccination
Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and six months after the primary course following challenge with PPV at six months post re-vaccination
Multisite Field Safety and Efficacy trial of a Porcine Parvovirus (PPV) killed vaccine in Spain

Laboratory trials

Four laboratory challenge studies were conducted. One study aimed to determine the minimum immunising dose but did not comply with the Ph. Eur. monograph 0965 and is therefore considered of limited value. The appropriate vaccine dose was determined in another study where the requirements set out in Ph. Eur. monograph 0965 were met. These criteria were also met in several laboratory studies. In all laboratory studies, vaccine batches with the minimum antigen content 1.0 µg/2 ml of the PPV VP2 antigen were used. In the supportive study also batches with 3.0 µg or 5.0 µg PPV antigen per 2-ml dose were used. Challenge was performed in all laboratory studies according to the Ph. Eur. monograph 0965, at about Day 40 of gestation. Gilts were thereafter euthanised at about the 90th gestation day, and the foetuses were examined for infection with PPV as demonstrated by presence of virus by PCR.

Minimum Immunizing Dose for a Killed *Erysipelothrix Rhusiopathiae* and Porcine Parvovirus (PPV) Subunit Vaccine when Administered to Gilts Pre-Breeding and Challenged with PPV at 40 Days of Gestation

This laboratory efficacy study aimed to establish the minimum immunising dose for the Porcine Parvovirus (PPV) fraction of a combination vaccine containing PPV and *Erysipelothrix rhusiopathiae* (Ery) serotype 2. The study included 60 seronegative gilts, 5—6 months old, randomised into five treatment groups (n=12) as follows: T01 were used as negative control and received placebo, T02 received Ery and low dose of PPV, T03 received Ery and medium dose of PPV, T04 received Ery and high dose of PPV and T05 received low dose of PPV. Gilts were given 2 ml of vaccine intramuscularly on D0 and D21. Post-vaccination, gilts were bred between D37 and D50 and challenged around gestation day 40. PPV infection was confirmed in 77% of the foetuses in the negative control group (placebo), and between 10–13% in the different treatment groups, thus, the study was not valid according to Ph. Eur. monograph 0965. As a result, no conclusions can be made with respect to efficacy of vaccination or the suitability of the different doses used from this trial.

Onset of immunity

One study was performed to investigate the onset of immunity.

Onset of immunity for a Porcine Parvovirus (PPV) subunit Vaccine

ReproCyc ParvoFLEX or ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU was administered twice to 5—6 months old seronegative gilts with a 3-week interval, with the last dose given three weeks

before mating. One group received ReproCyc ParvoFLEX only (n=27); one group received ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU as 1st treatment and ReproCyc ParvoFLEX alone as 2nd dose (n=27), and one group received placebo (n=27). One group served as untreated controls (n=3). Gilts were challenged at gestation day 40, except for the strict controls, which were not challenged. The proportion of foetuses protected against PPV infection was 95.7% in the group administered ReproCyc ParvoFLEX and 94.3% in the group administered the association of ReproCyc ParvoFLEX and ReproCyc PRRS EU, whereas 91.4% of foetuses in the placebo control group were PPV infected, as determined by PCR detection of the virus. The results showed an acceptable efficacy of vaccination according to the requirements of the Ph. Eur. monograph 0965 confirming the onset of immunity at the beginning of the gestation period.

Duration of immunity (DOI)

Two laboratory studies were performed in relation to DOI.

Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and challenged with PPV at 6 months and 12 months after vaccination

ReproCyc ParvoFLEX was administered twice with a 3-week interval to 5—6 months old seronegative gilts, with the last dose given three weeks before mating, and a single dose administered six months after the basic vaccination representing the proposed re-vaccination schedule. One group (n=16) received ReproCyc ParvoFLEX in accordance with the basic vaccination schedule, another group (n=16) received ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU, also following the basic vaccination schedule as proposed and a third group (n=12) received placebo. A fourth group (n=4) served as strict controls and did not receive any treatment. For re-vaccination, six months after basic vaccination, one group (n=16) received one dose of ReproCyc ParvoFLEX, and one group (n=12) received placebo. Furthermore, two gilts served as strict control group. Gilts were challenged 6 months after basic vaccination at gestation day 40, and six months after re-vaccination at gestation day 40. The primary outcome parameter was the percentage of PPV PCR-positive foetuses, which was 96.4% in the control group, while no PPV-positive foetuses were detected in either of the vaccinated groups, as determined by PCR detection of the virus, indicating 100% protection against PPV infection from vaccination in this study. The PPV viraemia status post-challenge and PPV serological status in gilts were secondary outcome parameters, and in piglets' foetal size, weight, and condition. 93-100% of vaccinated animals were seropositive at challenge, while all control animals remained seronegative. Viraemia was not detected in any of the vaccinated animals, while 100% of the control animals were positive after challenge. A reduction in number of abnormal foetuses was seen in vaccinated animals as compared to controls. In conclusion, the results showed an acceptable level of efficacy according to the requirements set out in Ph. Eur. monograph 0965 and duration of immunity of 6 months after basic vaccination and six months after re-vaccination.

Duration of immunity for a Porcine Parvovirus (PPV) subunit vaccine when administered to gilts pre-breeding and six months after the primary course following challenge with PPV at six months post re-vaccination

ReproCyc ParvoFLEX was administered twice to 5—6 months old seronegative gilts with a 3-week interval, with re-vaccination performed after six months. One group (n=17) received the PPV vaccine on D0, D21, and D210, while the control animals (n=16) received placebo. One group (n=6) served as strict controls and did not receive any treatment and were not challenged. Gilts were

mated twice during the study and challenged at approximately 40 days of gestation during the second pregnancy six months after re-vaccination. Challenge was performed in eight animals in the vaccinated group and nine in the control group. Foetuses from the second pregnancy were harvested at approximately 90 days of gestation. The proportion of PPV positive foetuses in the control group was 93% and in the PPV vaccinated group 2% as determined by PCR detection of the virus. The study fulfilled the criteria of Ph. Eur. monograph 0965 and the vaccine complied with the test as >80% of piglets were protected from infection. Duration of immunity six months after re-vaccination was confirmed.

Maternally derived antibodies (MDA)

No data have been presented in the dossier concerning the influence of maternal antibodies on the efficacy of the vaccine. The vaccine is, however indicated for treatment in gilts from 5 months of age when levels of MDA can be considered to be negligible.

Interactions

Efficacy of ReproCyc ParvoFLEX when used in association by mixing with the PRRS vaccine ReproCyc PRRS EU has been evaluated in two laboratory studies for basic vaccination and one field study for basic vaccination and re-vaccination. In the laboratory studies, efficacy was demonstrated in accordance with the requirements set out in Ph. Eur. monograph 0965 for both ReproCyc ParvoFLEX administered alone and in associated use with ReproCyc PRRS EU. Similarly, the outcome of the field study supports a comparable effect of ReproCyc ParvoFLEX when administered alone or in association with ReproCyc PRRS EU.

Two laboratory studies have been provided to demonstrate efficacy of ReproCyc PRRS EU during associated use with ReproCyc ParvoFLEX.

Onset of immunity and lack of interference study for a porcine parvovirus (PPV) subunit vaccine when co-administered with the commercial ReproCyc PRRS EU to breeding-age gilts and challenged with Porcine Reproductive and Respiratory Syndrome virus four weeks later.

ReproCyc PRRS EU was administered twice to 5—6 months old seronegative gilts with a 3-week interval, alone or in associated use mixed with ReproCyc ParvoFLEX. One group (n=12) received ReproCyc PRRS EU on D0 and D21, one group (n=12) received ReproCyc ParvoFLEX mixed with ReproCyc PRRS EU on D0 and ReproCyc ParvoFLEX only on D21, while the control animals (n=12) received placebo. Challenge with PRRS EU Isolate 190136, 5.54 $\log_{10}TCID_{50}$/6 mL dose, was performed on all animals on D28 (4 weeks after first vaccination). The challenge strain was used previously in studies submitted for the initial marketing authorisation application for ReproCyc PRRS EU and was considered relevant for the epidemiological situation of PRRSV in Europe at that time. The primary efficacy variable used in this study was a statistically significant reduction in the proportion of viraemia and viral load of PRRSV in gilts post-challenge, which was the same primary efficacy variable used in the initial marketing authorisation application for ReproCyc PRRS EU. A statistically significant reduction in the proportion and viral loads of PRRSV viraemic gilts for vaccinated gilts of both groups compared to control gilts post-challenge was demonstrated, and efficacy of the associated use of ReproCyc PRRS EU mixed with ReproCyc ParvoFLEX was established with an OOI of four weeks.

Duration of immunity and lack of interference study for a porcine parvovirus (PPV) subunit vaccine when co-administered with the commercial ReproCyc PRRS EU to breeding-age gilts and challenged with Porcine Reproductive and Respiratory syndrome virus at 90 Days of Gestation

ReproCyc PRRS EU was administered twice to 5—6 months old seronegative gilts with a 3-week interval. One group (n=28) received ReproCyc PRRS EU mixed with ReproCyc ParvoFLEX on D0, and ReproCyc ParvoFLEX only on D21, one group (n=28) served as negative controls and received placebo. One group (n=9) served as strict controls and did not receive any treatment and were not challenged. A group receiving ReproCyc PRRS EU alone was not included in the study. Challenge was performed on 16 animals in the vaccine group and 16 in the control group at D118 (at approximately 90 days of gestation), with PRRS EU Isolate 190136, 5.49 $\log_{10}TCID_{50}$/6 mL dose. The challenge strain was used previously in studies for the initial marketing authorisation for ReproCyc PRRS EU. The primary outcome parameters evaluated by qPCR 7 and 14 days post challenge were the proportion of viraemic gilts, the reduction of viral loads in gilt serum, and the duration of viraemia in gilts. Vaccinated gilts had significantly lower mean PRRSV viral load at 7 and 14 days post-challenge, and the proportion of PRRSV positive gilts was lower in the vaccinated group compared to controls. Vaccinated gilts had a significantly shorter duration of viraemia compared to control gilts. Vaccinated gilts had a significantly higher number and percentage of total live born piglets, healthy piglets, and piglets with a higher ADWG compared to controls.

However, due to the lack of a test group receiving ReproCyc PRRS alone, it is not possible to state a lack of interference from the associated use of the two vaccines.

The applicant has instead provided results from a previous study for comparison. This study was evaluated as a DOI study in the initial marketing authorisation application for ReproCyc PRRS EU. The study design, including vaccine dose, efficacy variables evaluated, challenge method and titre used, were similar between these studies. The outcome of most of the investigated variables were numerically comparable between groups administered a mix of both vaccines, and ReproCyc PRRS EU alone, in this study as well as in the other study.

Therefore, it can be accepted that the associated use by mixing of ReproCyc ParvoFLEX does not seem to interfere with the efficacy of ReproCyc PRRS EU at the end of the duration of immunity (17 weeks). The DOI claim of 17 weeks for ReproCyc PRRS EU remains valid for ReproCyc PRRS EU when used in association (mixed) with ReproCyc ParvoFLEX.

No data from field studies were included as grounds for approval in the initial market authorisation for ReproCyc PRRS EU; however, results from three field studies were submitted as part of the original application. Two of the studies were accepted as being supportive only, and in the last study there was no statistically significant difference for the primary efficacy variable between vaccinated animals and controls. In the light of this, it is not deemed necessary to include further field data to establish a lack of interference from the associated use of ReproCyc PRRS EU mixed with ReproCyc ParvoFLEX on the efficacy of ReproCyc PRRS EU.

Field trials

One multicentre, randomised, blinded, active-controlled study was conducted at three sites in Spain. In the first phase of the study, basic vaccination with two administrations of ReproCyc ParvoFLEX at an intermediate antigen dose with a 3-week interval as proposed for basic vaccination was evaluated. In a second phase, revaccination with a single administration after six months was evaluated.

ReproCyc ParvoFLEX was administered to two groups of animals, either as only treatment or as associated by mixing with ReproCyc PRRS EU. Pigs in the control group were vaccinated with a comparator PPV vaccine (Parvoseng) currently registered in the EU.

The main primary efficacy parameter was the proportion of mummified piglets per litter in the treatment groups. Secondary efficacy parameters included the reproductive performance of the sows, number and proportion of piglets per litter at weaning and seroconversion to PPV and collection of tissue samples from litters with more than two mummified foetuses or stillborn piglets.

The results of the field trial showed that the administration of ReproCyc ParvoFLEX, alone or in associated use (mixed) with ReproCyc PRRS EU, to gilts and sows according to the recommended vaccination schedule resulted in comparable results between groups regarding all efficacy parameters.

Overall conclusion on efficacy

The proposed vaccination schedule includes a basic vaccination of two administrations given with a three-week interval with the last dose administered three weeks before mating. Re-vaccination is proposed as one dose of vaccine every 6 months in a whole herd programme. Onset of immunity has been demonstrated from the beginning of the gestation period and duration of immunity was shown 6 months after basic vaccination and after re-vaccination.

The results from three laboratory studies performed in accordance with the requirements of Ph. Eur. monograph 0965 indicate that ReproCyc ParvoFLEX is effective against transplacental porcine parvovirus infection, since > 80% of the total number of piglets from vaccinated gilts were protected from infection, as demonstrated by absence of the virus by PCR detection.

One field study was performed in three centres in Spain. In the study, ReproCyc ParvoFLEX was compared to an authorised vaccine against PPV, and the results generally indicated that the level of efficacy as demonstrated in the study was comparable between the two vaccines.

In the clinical studies, it was demonstrated that vaccination protects the progeny from infection with PPV and thereby reduces losses due to reproductive disorders associated with parvovirus infection.

The claim for an associated use by mixing of ReproCyc ParvoFLEX and ReproCyc PRRS EU has been adequately supported.

Part 5 – Benefit-risk assessment

Introduction

ReproCyc ParvoFLEX is an inactivated vaccine for the immunisation of gilts and sows from the age of 5 months to protect progeny against transplacental infection caused by porcine parvovirus.

ReproCyc ParvoFLEX contains the PPV 27a viral protein 2 (VP2) as active substance, carbomer as adjuvant, and sodium chloride and water for injections as excipient. The active substance of ReproCyc ParvoFLEX is the VP2 protein, a new active substance not authorised for a veterinary medicinal product in the EU before.

The proposed vaccination scheme is two injections of one dose by an interval of 3 weeks.

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

Benefit assessment

Direct therapeutic benefit

The benefit of ReproCyc ParvoFLEX is its efficacy in protecting the offspring against transplacental PPV infection which was established in a sufficient number of well-designed laboratory and field studies conducted to an acceptable standard.

A clinical field trial conducted in accordance with GCP requirements was performed to show efficacy and safety in a field setting; the results show that the protection, measured as percentage of mummified piglets per litter, was comparable to the comparator group.

The onset of immunity is shown to be from the beginning of the gestation period, when gilts are vaccinated with two intramuscular injections of one dose of the vaccine, 3 weeks apart. The duration of immunity was shown to be six months after primary vaccination, and six months after re-vaccination (at six months after primary vaccination).

The therapeutic benefit for the offspring is documented, and the disease is of major economic importance.

Additional benefits

ReproCyc ParvoFLEX increases the range of available treatment possibilities against PPV infection.

Risk assessment

Quality:

Information on the development, manufacture, starting materials and control of the active substance and the finished product has been presented in a satisfactory manner.

Safety:

Risks for the target animal:

Administration of ReproCyc ParvoFLEX in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include local reactions such as transient redness and swelling, which are very common, and resolve within two to five days without treatment. An elevation in the body temperature after vaccination is common which resolves spontaneously within 24 to 48 hours. Safety of the use during pregnancy and lactation has been adequately demonstrated.

Risk for the user:

There are no unacceptable risks identified for the user of ReproCyc ParvoFLEX when used in accordance with the SPC. The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection. The active substance is an inactivated protein and is not infectious. The excipients including adjuvants are commonly used in other vaccines and do not pose a risk for the user.

Risk for the environment:

ReproCyc ParvoFLEX is not expected to pose a risk for the environment when used according to the SPC.

Risk for the consumer:

The withdrawal period is set at zero days.

Risk management or mitigation measures

Adequate risk management or mitigation measures to ensure the safe and effective use of the product have been included in the SPC.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the active immunisation of gilts and sows from the age of 5 months to protect progeny against transplacental infection caused by porcine parvovirus.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for ReproCyc ParvoFLEX is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).