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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ENTEROPORC AC

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0271/001/DC
Name, strength and pharmaceutical form	Enteroporc AC Lyophilisate and solvent for suspension for injection for pigs
Applicant	IDT Biologika GmbH Am Pharmapark 06861 Dessau-Rosslau Germany
Active substance(s)	One dose (2 ml of the reconstituted vaccine) contains: *Clostridium perfringens* type A toxoid: alpha toxoid min. 125 rU*/ml beta2 toxoid min. 770 rU*/ml *Clostridium perfringens* type C toxoid: beta1 toxoid min. 3354 rU*/ml * relative Units
ATC Vetcode	QI09AB12
Target species	Pigs (pregnant sows and gilts)
Indication for use	For the passive immunisation of progeny by active immunisation of sows and gilts to reduce mortality and clinical signs during the first days of life caused by *Clostridium perfringens* type A associated enteritis and necrotising enteritis induced by *Clostridium perfringens* type C.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12 (3) and Article 32 (3) of Dir. 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28 June 2017
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	AT, BE, CZ, DK, ES, FR, HU, IE, IT, NL, PL, PT, RO, SK, UK

I. SCIENTIFIC OVERVIEW

Enteroporc AC is intended for the passive immunisation of progeny by active immunisation of sows and gilts to reduce mortality and clinical signs during the first days of life caused by *Clostridium perfringens* type A associated enteritis and necrotising enteritis induced by *Clostridium perfringens* type C.

The vaccine consists of the lyophilised *C. perfringens* type A and C toxoids and an associated solvent containing water for injection (WFI), the adjuvant Montanide Gel and thiomersal as preservative. The active ingredients are the toxoids of alpha, beta1 and beta2 toxins.

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The freeze-dried vaccine contains:

Active substances:

Clostridium perfringens type A/C toxoids:

alpha toxoid	min. 125 rU/ml*
beta1 toxoid	min. 3354 rU/ml*
beta2 toxoid	min. 770 rU/ml*

*toxoid content in relative units per ml, determined in ELISA against an internal standard

The solvent contains:

Montanide Gel (adjuvant)	37.4 – 51.5 mmol/l titratable acrylate units
Thiomersal (preservative)	0.085 – 0.115 mg/ml

The vaccine (lyophilisate) is filled in 10 ml glass injection bottles, glass type I, closed with bromobutyl rubber stoppers. The solvent is filled in 25 ml glass or 50 ml glass injection bottles closed with bromobutyl rubber stoppers. The material complies with the requirements of the European Pharmacopoeia.

The choice of the adjuvant Montanide gel, the vaccine strains selected and the presence of the preservative thiomersal are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with pharmacopoeia monographs where these exist or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control Tests during Production

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests included:

Test on the concentrate

Glutaraldehyde* ≤ 0.5 mg/ml

* The determination of glutaraldehyde is tested as an in-process control relevant to the finished product

Tests on the lyophilisate:

Appearance

Residual moisture

Sterility

Tests on the solvent:

Appearance

pH value

Sterility

Montanide Gel

Thiomersal

Tests after resuspension

Appearance

pH value

Montanide Gel

Thiomersal

Reconstitution time

Alpha toxoid content

Beta1 toxoid content

Beta2 toxoid content

The demonstration of the batch-to-batch consistency is based on the results of three batches produced according to the method described in the dossier.

F. Stability

Stability data on the active substances have been provided demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (24 months for the lyophilisate, 27 months for the solvent) and when stored under the approved conditions (storage below 25 °C).

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

III. SAFETY ASSESSMENT

Enteroporc AC is an inactivated *Clostridium perfringens* type A and type C toxoid vaccine for pigs. Active ingredients are the toxoids of the alpha, beta1 and beta2 toxin, which play a role in the pathogenesis of the *C. perfringens* type A associated enteritis and the necrotic enteritis caused by *Clostridium perfringens* type C. The vaccine is intended for intramuscular injection to pregnant sows and gilts. The aim of the active immunisation of sows is the passive immunisation of suckling pigs via maternal antibodies against the alpha, beta1 and beta2 toxin. Montanide Gel is used as adjuvant in the vaccine.

Laboratory Trials

Three laboratory studies have been performed to test the safety on reproductive performance. These studies include the safety testing of the administration of one dose in 12 vaccinated and 10 control sows and the repeated administration of one dose in two studies with 46 gilts. As it is intended to revaccinate gilts and sows with primary immunisation prior to subsequent farrowing, the administration of three single doses was also tested.

The investigation was performed according to the recommendations of "Guideline on Data requirements for Immunological veterinary medical products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/ 123243/2006-Rev.2)" and the Ph. Eur. monograph "*Clostridium perfringens* vaccine for veterinary use".

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny. Therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant Montanide is listed in Annex to EU Regulation 37/2010 (Table 1) and considered safe as the adjuvants listed there are approved for use in food-producing animals with no need for details on maximum residue limits. Thiomersal is listed in Annex (Table 1) to EU Regulation 37/2010 and is approved for use in food-producing target species. It is allowed for use as a preservative in multidose vaccines at a concentration not exceeding 0.02 %. The thiomersal proportion in Enteroporc AC is 0.01%.

Based on this information, no withdrawal period is proposed.

Overall, the vaccine proved to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under "adverse reactions". Since swellings may occur at the injection site, special warnings for the user after possible self-injection are included in the instructions for use.

In 3 laboratory studies the vaccination had no negative impact on the reproductive performance of the sows as described in the SPC.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Details are given in the Summary of Product Characteristics (SPC) as follows:

4.6 Adverse reactions (frequency and seriousness)

Slight increases in body temperature (in individual cases a maximum increase of 2.4 °C) on the day of vaccination are very common.
Local reactions (flat swellings, with a maximum diameter of 10 cm in isolated cases) at the injection site are very common, but subside without treatment within 14 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Can be used during pregnancy.

4.8 Interaction with other medicinal products and other forms of interaction

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Field Studies

Three field studies were performed to assess the safety of the vaccine.

Two field trials were carried out simultaneously. In the first trial, 18 gilts were immunised twice at intervals of three weeks with a single dose (17 gilts were used as control gilts) and in the second trial, 24 gilts were immunised three times (25 gilts were used as control gilts). In a further field trial, 9 sows from the second field trial (9 sows were used as control sows) were vaccinated a fourth time, two weeks before the 3rd farrowing. In all trials, the safety and reproductive performances were tested.

All animals were observed for local or systemic reactions during the studies.

Overall, the vaccine Enteroporc AC proved to be well tolerated in the target species. The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under “adverse reactions”.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that Enteroporc AC contains neither viable nor inactivated microorganisms that could be transmitted to the user or to the animal. The use of the vaccine does not lead to any residues that could cause harm to the consumer. As such, no withdrawal period needs to be considered between use of the vaccine, the time of slaughtering and the final release for human consumption. The vaccine is assessed as safe for animals, users and the environment.

IV. EFFICACY

IV.B Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the "Guideline on Data requirements of Immunological veterinary medical products intended for minor use or minor species/limited market (EMA/CVMP/IWP/123243/2006-Rev.2)", Ph. Eur. monograph "*Clostridium perfringens* vaccine for veterinary use" and the Directive 2001/82/EC as amended, which included:

- the development of *in vitro* methods for the detection of the immune response to alpha, beta1 and beta2 toxins,
- the development of an alpha and beta2 intoxication model as well as a beta1 intoxication model to test the efficacy of test batches,
- the verification of the immunogenicity of the vaccine and of a correlation between the antigen content (beta1 toxoid) and the efficacy,
- investigations of onset and duration of immunity,
- studies of the recommended vaccination scheme and route of administration,
- efficacy testing according to the monograph "*Clostridium perfringens* vaccine for veterinary use" (EP).

In the laboratory studies the gilts and sows were vaccinated with the vaccine Enteroporc AC in accordance with the instructions for use. The studies were divided into two parts. The first part included the vaccination of the gilts and sows and the serological examination of sera and colostrum. Intoxication of the piglets was carried out in the second part.
In the trials, the vaccine Enteroporc AC was adjusted to the lower alpha and beta2 toxoid content and also to the lower beta1 toxoid content. At the same time, a medium for resuspension was used that was adjusted to the lower thiomersal and adjuvant content. After two vaccinations of gilts a significant increase in antibodies against the alpha, beta1 and beta2 toxins in the serum at farrowing was seen in all trials. These antibodies were also enriched in the colostrum. In both the alpha/beta2 toxin challenge and in the beta1 toxin challenge piglets were protected against intoxication with the toxin of a heterologous *C. perfringens* type A and C strain after colostrum uptake. After third vaccination of the gilts (two weeks before the next farrowing) significantly higher antibody levels against the alpha, beta1 and beta2 toxins occurred compared to those after primary immunisation.

Four studies were conducted on the detection of immunogenicity with reference to the dose response relationship. One study was conducted for alpha and beta2 toxoid and three trials for the beta1 toxoid. Pregnant gilts and sows were vaccinated with the *C. perfringens* type A/C vaccine. A corresponding control group was administered a placebo. After birth and take up of colostrum two piglets per sow were challenged with the alpha and beta2 toxins of a *C. perfringens* type A strain and with the beta1 toxin of a *C. perfringens* type C strain.
The clinical parameters of the piglets were evaluated and the number of animals that died was recorded. Blood and colostrum samples were taken from the sows. The lower effective dose for the alpha toxoid (125 rU/ml) and the beta2 toxoid (770 rU/ml) was already determined during development of the vaccines Clostriporc A and Enteroporc A and in one study during development of the vaccine Enteroporc AC. The use of the vaccine Enteroporc AC adjusted to 125 rU alpha toxoid/ml protected piglets via colostral antibody transmission against intoxication with a *C. perfringens* type A strain. The level of antibodies against the alpha and beta2 toxins in the serum and colostrum showed a

significant increase in all vaccinated sows. The use of the vaccine Enteroporc AC adjusted to 3354 rU/ml beta1 toxoid protected piglets via colostral antibody transmission against intoxication with a *C. perfringens* type C strain. The level of antibodies against the beta1 toxin in serum and colostrum showed a significant increase in all vaccinated sows.

In one trial the vaccine Enteroporc AC adjusted to the lower beta1 toxoid and adjuvant content was tested for efficacy on rabbits in accordance with the Ph. Eur. monograph "Clostridium perfringens vaccine for veterinary use". For this, antibodies against the beta1 toxin were investigated in pooled rabbit serum. An antibody level of 41 IU/ml in pooled serum against the beta1 toxin was shown. Thus the measured content was higher than the level required by the Ph. Eur. monograph. As such, the vaccine Enteroporc AC (adjusted to the lower beta1 toxoid and adjuvant content) meets the requirements of the Ph. Eur. monograph "Clostridium perfringens vaccine for veterinary use"

The following conclusions regarding onset and duration of immunity, indications for use and immunisation scheme can be drawn from the results of the laboratory studies:

For the passive immunisation of progeny by active immunisation of sows and gilts to reduce mortality and clinical signs during the first days of life caused by *Clostridium perfringens* type A associated enteritis and necrotising enteritis induced by *Clostridium perfringens* type C.

Onset of immunity:
This protection was proven in a challenge test with toxins on suckling piglets on the first day of life.

Duration of immunity:
Serological data show that neutralising antibodies are present up to the 2nd week after birth. The presence of neutralising antibodies has been shown to correlate to protection.

Primary vaccination of pregnant sows before farrowing:
Administer a single dose 5 weeks and 2 weeks before the expected date of farrowing.

Primary vaccination of gilts before insemination:
Administer a single dose 7 weeks and 4 weeks before insemination, and 2 weeks before the expected date of farrowing.

Revaccination:
Administer a single dose 2 weeks before the expected date of each subsequent farrowing.

Field Trials

In three field trials, gilts and sows were immunised with Enteroporc AC.

In the first trial, 18 gilts were vaccinated twice at intervals of three weeks with a single dose (five and two weeks before farrowing). 17 gilts were used as control. Efficacy was evaluated on the basis of the development of antibodies against alpha, beta1 and beta2 toxins in serum and colostrum, the compilation of mortality, the incidence of diarrhoea and body weight increase.

In the second trial, 24 gilts were vaccinated three times (25 gilts were used as control) with one dose seven and four weeks before insemination and a third time two weeks before the first farrowing. The development of antibodies against alpha, beta1 and beta2 toxins in the serum and colostrum were compared with the vaccination given twice (laboratory trials).

In a third field trial, nine sows from the second field trial (nine sows were used as control) were vaccinated a fourth time, two weeks before the third farrowing. The development of antibodies against alpha, beta1 and beta2 toxins in the serum and colostrum were compared with the results after three times vaccination (laboratory trials).

The vaccine scheme was confirmed by the field trials performed. In the field trials significantly higher antibody levels against the alpha, beta1 and beta2 toxins were shown after vaccination compared to the control group. At the same time the vaccination significantly reduced the incidence of diarrhoea (*C. perfringens* type A) in the piglets of vaccinated sows.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that the benefit-risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable when the product is used in accordance with the Summary of Product Characteristics.