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MUTUAL RECOGNITION PROCEDURE
MUMS PRODUCT

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CLOSTRIPORC A

***Clostridium perfringens* type A – toxoid vaccine, for pigs (pregnant sows and gilts)**

PRODUCT SUMMARY

EU Procedure number	DE/V/0262/001/MR
Name, strength and pharmaceutical form	Clostriporc A *Clostridium perfringens* type A – toxoid vaccine, for pigs (pregnant sows and gilts) Suspension for injection for subcutaneous use
Applicant	IDT Biologika GmbH Am Pharmapark 06861 Dessau-Roßlau Germany
Active substance(s)	One vaccine dose (2 ml) contains: **Immunologically active substance** *Clostridium perfringens* type A toxoids: alpha toxoid min. 125 rU*/ ml beta2 toxoid min. 770 rU* /ml * toxoid content in relative units per ml, determined in ELISA against an internal standard **Adjuvant** Montanide Gel 37.4-51.5 mmol/l titratable acrylate units **Excipients** Thiomersal 0.2 mg
ATC Vetcode	QI09AB12
Target species	pigs (pregnant sows and gilts)
Indication for use	For the passive immunisation of piglets by active immunisation of pregnant sows and gilts to reduce clinical signs during the first days of life caused by *Clostridium perfringens* type A expressing alpha and beta2 toxins. This protection was proven in a challenge test with toxins on sucklers on the first day of life. Serological data show that neutralising antibodies are present up to the 4th week after birth.

Summary of Product Characteristics

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CLOSTRIPORC A
Suspension for injection for pigs (pregnant sows and gilts)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (2 ml) contains:

Active substances:
Clostridium perfringens type A toxoids:

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

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

Adjuvant:

Montanide Gel	37.4 – 51.5 mmol/l titratable acrylate units

Excipient:

Thiomersal	0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Appearance after mixing: amber, opaque liquid

4. CLINICAL PARTICULARS

4.1 Target species

Pigs (pregnant sows and gilts)

4.2 Indications for use, specifying the target species

For the passive immunisation of piglets by active immunisation of pregnant sows and gilts to reduce clinical signs during the first days of life caused by *Clostridium perfringens* type A expressing alpha and beta2 toxins. This protection was proven in a

challenge test with toxins on sucklers on the first day of life. Serological data show that neutralising antibodies are present up to the 4th week after birth.

4.3 Contraindications

Do not use in clinically sick or severely stressed animals.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

To the user:
This veterinary medicinal product contains traces of mineral oil as constituent of Montanide Gel. Accidental injection/self-injection may result in severe pain and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given. If you are accidentally injected with this product, seek prompt medical advice even if only a very small amount is injected and take the package leaflet with you. If pain persists for more than 12 hours after medical examination, seek medical advice again.

To the physician:
This veterinary medicinal product contains traces of mineral oil as constituent of Montanide Gel. Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even the loss of a digit.
Expert, prompt, surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon.

4.6 Adverse reactions (frequency and seriousness)

Very commonly slight increases in body temperature (up to max. 1.8 °C) on the day of vaccination are possible.
Very commonly local reactions may be observed in the form of flat swellings (diameter up to max. 10 cm) at the injection site, but subside without treatment within 12 days.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one
  treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports)

4.7 Use during pregnancy and lactation

CLOSTRIPORC A is intended for the immunisation of pregnant sows and gilts.

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.

4.9 Amounts to be administered and administration route

For subcutaneous use.

Primary immunisation:
1. Immunisation: 2 ml *s.c.* 5 weeks before the expected date of farrowing
2. Immunisation: 2 ml *s.c.* 2 weeks before the expected date of farrowing

Revaccination:
One immunisation: 2 ml *s.c.* 2 weeks before the expected date of farrowing

Shake vaccine well before use.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After administration of the double dose no other symptoms other than those described at point 4.6 were observed.

4.11 Withdrawal period

Zero days.

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Immunologicals for suidae, inactivated bacterial vaccines.
ATCvet code: QI09AB12

The active immunisation of pregnant sows and gilts induces the formation of antibodies against the alpha and beta2 toxins of *Clostridium perfringens* type A.
The uptake of sufficient antibodies at the earliest opportunity, via the colostrum, results in a passive protection of the sucklers against the effects of the alpha and beta2 toxins of *Clostridium perfringens* type A.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Montanide Gel
Thiomersal
Glutaraldehyde
Water for injections

6.2 Incompatibilities

Do not mix with any other veterinary medicinal product.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Shelf life after first opening the immediate packaging: 8 hours. Between removals the vaccine should be stored at +2 °C - +8 °C.

6.4. Special precautions for storage

Protect from light. Store and transport refrigerated (+2 °C - +8 °C). Protect from frost.

During storage increased turbidity of the suspension and a slight, black precipitation may occur which have no impact on the efficacy, safety and quality of the product.

6.5 Nature and composition of immediate packaging

Type II colourless glass vials of 50 and 100 ml.
Polyethylenterephthalate (PET) bottles of 50 and 100 ml.
The bottles are closed with a bromobutyl rubber stopper and crimped cap.
Package sizes:

Cardboard box with 1 glass vial of 25 doses (50 ml)
Cardboard box with 1 glass vial of 50 doses (100 ml)

Cardboard box with 1 PET vial of 25 doses (50 ml)
Cardboard box with 1 PET vial of 50 doses (100 ml)

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

IDT Biologika GmbH
Am Pharmapark
06861 Dessau-Rosslau
Germany

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

10 DATE OF REVISION OF THE TEXT

MM/YYYY

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

PUBLICLY AVAILABLE ASSESSMENT REPORT

Legal basis of original application	MRP application in accordance with Article < > of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	18.06.2014
Date product first authorised in the Reference Member State (MRP only)	24.11.2011
Concerned Member States for original procedure	BE; CZ; DK; ES;FR; NL; PL; SK

I. SCIENTIFIC OVERVIEW

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

Active substances:

Clostridium perfringens type A toxoids:

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

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

Adjuvant:

Montanide Gel	37.4 – 51.5 mmol/l titratable acrylate units

Excipient:

Thiomersal	0.2 mg

Container/closure device:

Glass and polyethylene terephthalate (PET) injection vials (with 50 or 100 ml).

The characteristics of the containers and the control tests performed are provided and conform to the regulations.

The choice of the adjuvant (Montanide Gel 1 PR), vaccine strain, and inactivation agent (glutaraldehyde) and the presence of preservative (thiomersal) is 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 fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of starting materials

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

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines.

The master and working seeds have been produced as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or 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.

E. Control tests during production

The tests performed during production are described in detail.
The following tests are carried out during production:

- pH measurement
- Sterility test according per USP and Ph. Eur.
- Purity test
- Check of growth
- Determination of alpha toxin (toxoid) content
- Determination of beta2 toxin (toxoid) content
- Test for residual toxicity
- Test of filling weight

F. Control tests on the finished product

The tests performed on the final product conform to the relevant requirements:

- visual inspection
- pH value
- determination of Montanide Gel
- determination of thiomersal content
- determination of glutaraldehyde content
- test for sterility of finished product
- determination of alpha toxoid content
- determination of beta2 toxoid content

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product (18 months) throughout its shelf life when stored under the approved conditions (cooled at 2-8 °C).

The claim of an eight-hour stability after broaching is based on data presented. Between removals the vaccine should be stored at +2 °C to +8 °C.

III. SAFETY ASSESSMENT

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

Laboratory trials

The following laboratory trials have been performed in the target species (pig):

- safety of the single administration of one dose
- safety of the administration of an overdose (double dose)
- safety of the repeated administration of one dose

The single and repeated administration of one dose and the administration of an overdose (double dose) have been tested. As primary immunised sows shall receive further booster vaccinations prior to next farrowing, the threefold administration of a single dose was also tested.
The animals were divided into groups and received either a single dose, a double dose or repeated single doses at intervals of several weeks.
Unvaccinated animals were used as controls. All animals were examined for local or systemic reactions during the study. Overall, CLOSTRIPORC A proved to be well-tolerated by the target species pig.

The local and systemic reactions observed are described under “Adverse reactions” in the Summary of Product Characteristics (SPC) and the package leaflet.
The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

As CLOSTRIPORC A is intended for the treatment of pregnant and lactating sows, 6 studies were performed in this regard.

As the toxoids of *C. perfringens* do not have any immunosuppressive properties, no study on immunological properties was carried out.

It is known that occasionally local reactions may occur after vaccination. This is also described in SPC and package leaflet.

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

No information on safety and efficacy are available when the product is administered simultaneously with another veterinary medicinal product. A corresponding warning is included in SPC and package leaflet.

Field trials

In two field trials, young and old sows were immunised twice with a single dose at an interval of three weeks and examined for safety and reproductive performance.
Unvaccinated animals were used as controls. All animals were examined for local and systemic reactions during the studies.
Overall, CLOSTRIPORC A proved to be well-tolerated by the target species pig. The results confirm the observations from the laboratory studies. The local and systemic reactions observed are included under „Adverse reactions“ in SPC and package leaflet.

Ecotoxicity

CLOSTRIPORC A does not represent a significant risk for the environment. The toxoid vaccine neither contains microorganisms capable of replication.
Spread of the production strain is therefore impossible, which is confirmed by the test for sterility within the scope of batch testing.
The mercury contained in the vaccine’s adjuvant Thiomersal is a rather undesirable substance as regards its ecotoxicity. However, CLOSTRIORC A contains only very small amounts of this substance and accidental spreading in the environment is unlikely, as the product is marketed only in relatively small containers and used only under controlled conditions. The vaccine’s other components neither represent a risk potential for the environment.
Overall, CLOSTRIPORC A is considered safe for animals, the user and the environment.

IV. EFFICACY

IV.B Laboratory trials

Laboratory studies to demonstrate the efficacy of the product were performed in compliance 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)".

The efficacy for the target species pig was demonstrated by means of an intoxication test in piglets and serological tests. In these studies, pregnant sows were vaccinated with CLOSTRIPORC A and their offspring was challenged with alpha and beta2 toxin after birth. Piglets of unvaccinated animals served as controls.
In serological tests the content of antibodies against the alpha and beta2 toxin in serum and colostrum of the sows was determined. The duration of immunity was tested by means of the antibody content in the piglets‘ sera. The results demonstrate the efficacy of CLOSTRIPORC A based on the recording of losses, the occurrence of diarrhoea and the live weight gain of the piglets.

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 piglets by active immunisation of pregnant sows and gilts to reduce clinical signs during the first days of life caused by *Clostridium perfringens* type A expressing alpha and beta2 toxins.
The uptake of sufficient antibodies at the earliest opportunity via the colostrum results in a passive protection against the effects of alpha und beta2 toxins of *C. perfringens* type A.
This protection was proven in a challenge test with toxins on sucklers on the first day of life. Serological data show that neutralising antibodies are present up to the 4th week after birth.

Immunisation scheme:

The vaccine CLOSTRIPORC A is intended for subcutaneous injection. It is administered as follows:

Primary immunisation

1. Immunisation: 2.0 ml *s.c.* 5 weeks *ante partum*
2. Immunisation: 2.0 ml *s.c.* 2 weeks *ante partum* and as

Booster immunisation of primary immunised sows

One immunisation: 2.0 ml *s.c.* 2 weeks *ante partum*

Field trials

In two field trials young and old sows were vaccinated twice with one dose at an interval of three weeks. The efficacy was examined based on the recording of losses, the occurrence of diarrhoea and the live weight gain of the piglets.
Depending on the state of immunity of the livestock the percentage of piglets suffering from diarrhoea decreased resulting in an improved weight gain of the animals.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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