Institute for State Control of Veterinary Biologicals and Medicines
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Czech Republic
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fencovis suspension for injection
(AT, BE, CZ, DE, EL, ES, FR, IE, IT, LU, NL, PT, UK(NI))

Fencovis RCE vet suspension for injection
(FI, NO, SE)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0177/001/DC
Name, strength and pharmaceutical form	**Fencovis suspension for injection (AT, BE, CZ, DE, EL, ES, FR, IE, IT, LU, NL, PT, UK(NI))** **Fencovis RCE vet suspension for injection (FI, NO, SE)**
Applicant	Boehringer Ingelheim Vetmedica, GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany
Active substance(s)	Inactivated *E. coli* expressing F5 (K99) adhesin, strain O8:K35 Inactivated bovine rotavirus, serotype G6P1, strain TM-91 Inactivated bovine coronavirus, strain C-197
ATC Vetcode	QI02AL01
Target species	Cattle (pregnant heifers and cows)
Indication for use	Active immunisation of pregnant heifers and cows in order to stimulate the development of antibodies against bovine rotavirus, bovine coronavirus and *E. coli* expressing F5 (K99) adhesin and to increase the level of passive immunity of calves against neonatal diarrhoea caused by bovine rotavirus, bovine coronavirus and *E. coli* expressing F5 (K99) adhesin. In calves fed with colostrum and milk from vaccinated cows for the first week of life, laboratory studies conducted with heterologous challenge strains (a G6 BRV strain, a BCV strain and a K99 *E. coli* strain) have demonstrated that these antibodies: - prevent neonatal diarrhoea caused by bovine rotavirus and *E. coli* expressing F5 (K99) adhesin, - reduce the incidence and severity of neonatal diarrhoea caused by bovine coronavirus, - reduce faecal shedding of virus in calves infected with bovine rotavirus and bovine coronavirus.

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	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25/05/2022
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	RMS: CZ CMS: AT,BE,DE,EL,ES,FI,FR,IE,IT,LU,NL,NO,PT,SE,UK(NI)

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, the consumer of foodstuffs from treated animals 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. Qualitative and quantitative particulars

Each 2 ml dose contains:
Active substances:

Inactivated *E. coli* expressing F5 (K99) adhesin, strain O8:K35	RP ≥ 1*
Inactivated bovine rotavirus, serotype G6P1, strain TM-91	RP ≥ 1*
Inactivated bovine coronavirus, strain C-197	RP ≥ 1*

* Relative potency (RP): level of antibodies in sera of vaccinated guinea pigs as determined by ELISA in comparison with the reference serum obtained after vaccination of guinea pigs with a vaccine batch that has successfully passed the challenge test in the target animals.

Adjuvants:

Aluminium hydroxide	6 mg
Quillaja saponin (Quil A)	≤ 0.4 mg

Excipients:

Thiomersal	0.2 mg
Formaldehyde	≤ 1 mg

The container/closure system

Type I glass vials of 3 or 10 ml with chlorobutyl elastomer closure and aluminium or flip off caps.
Type II glass vials of 50 or 100 ml with chlorobutyl elastomer closure and aluminium or flip off caps.
Translucent plastic (HDPE) vials of 15, 60 or 120 ml with chlorobutyl elastomer closure and aluminium or flip off caps.

Plastic box of 2, 10 or 20 glass vials of 1 dose (2 ml)
Cardboard box of 1 glass or plastic vial of 5 doses (10 ml)
Plastic box of 5 or 10 glass or plastic vials of 5 doses (10 ml)
Cardboard box of 1, 12 or 24 glass or plastic vials of 25 doses (50 ml)
Cardboard box of 1 glass or plastic vial of 50 doses (100 ml)

The choice of the adjuvants, vaccine strains, inactivating agent and presence of preservative 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 fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.

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 indicate pharmacopoeia monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs or in-house specifications and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. monographs.

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

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.

D. Control tests during production

The tests performed during production are described in detail and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product confirm the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.

The tests include in particular:
- appearance
- sterility
- air tightness
- extractable volume
- pH
- potency*
- identity*
- aluminium content*
- thiomersal content*
- endotoxins assay **
- formaldehyde content*
- Quillaja saponin content*

*performed as an in-process control on bulk vaccine
**performed on bacterin just before vaccine bulk formulation

F. Batch to batch consistency

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

For the Bovine rotavirus antigen and the Bovine coronavirus antigen after inactivation was verified the period of storing at the temperature 2-8 °C for max. 1 month and/or at -20 °C for max. 12 months.

For the *E. coli* antigen after inactivation was verified the period of storing at the temperature 2-8 °C for 6 months.

Based on the results of the tests of the vaccine, the stability of bulk of the vaccine for 1 month was demonstrated when stored under the approved conditions 2-8 °C.

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 (2 years) when stored under the approved conditions (2-8 °C).

The in-use shelf-life of the broached vaccine (10 hours) is supported by the data provided.

G. Other Information

Not applicable.

III. SAFETY ASSESSMENT

The vaccine is administered intramuscularly as single dose (2 ml) to pregnant cows and heifers at each pregnancy, 3 to 12 weeks before the expected date of calving.

Safety studies have been performed with a vaccine batch with maximum antigen content produced according to the described production process.

Field studies have been performed with a representative vaccine batch produced according to the described production process.

Laboratory trials

One controlled laboratory study was performed to evaluate the safety of one dose and the repeated administration of one dose. The study was performed taking into account the requirements of Ph. Eur. 5.2.6. and included 20 animals (10 vaccinated animals and 10 unvaccinated animals) in total. One group of 5 animals was first vaccinated 11 weeks (±1 week) apart from delivery and vaccinated again two weeks later. Another group of 5 animals was vaccinated at 4 weeks (±1 week) before the expected date of delivery and revaccinated two weeks later.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. Rectal temperatures, general health status and local reactions were observed.
The safety studies demonstrate that the administration of one dose and the repeated administration of a dose can be considered to be safe, when used in accordance with the recommended vaccination schedule. The observed reactions are reflected in the relevant SPC and package leaflet sections:

"An increase in mean body temperature of 1.0°C was very commonly observed in laboratory and field studies; in individual cases, the maximum increase may reach 2.1°C, with body temperatures resolving to normal levels within 2 days without impairing the general health status of the vaccinated animals."

Effects on reproductive performance were examined in addition. No effect on the reproductive performance and on the health status of the new born calves was observed. Accordingly, the wording in the SPC:

"Can be used during pregnancy.
The effect of vaccination on pre- or post-partum lactation was not studied."

Is regarded suitable.

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 and excipients used are aluminium hydroxide, quillaja saponin (Quil A), formaldehyde and thiomersal. The excipient and adjuvants are included in the Appendix of the Commission Regulation (EU) No 37/2010 – the substances that are not subject to determination of residues. For

this reason, the presence of the residues was not tested. Based on this information, no withdrawal period is proposed.

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

Field studies

A combined safety and efficacy field trial was performed on target animals.
The vaccine was administered to cows/heifers according to the scheme mentioned in the SPC.
A total number of 90 pregnant cows/heifers were selected on three farms 12-3 weeks before the expected date of calving. Animals were randomly allocated to groups, so that there were 20 vaccinated and 10 control animals on each farm.
The safety evaluation was based on: observation of local and systemic reactions, measurement of rectal temperatures and evaluation of general health state.
Calves were fed the colostrum and milk from their mothers (vaccinates and controls) and monitored from the day of birth until 14 days later.
The safety of the vaccine in cows/heifers and calves in the field has been demonstrated. The results from the field trial basically confirm those observed in the laboratory study. The additionally observed local reactions are reflected in the SPC:

A localised mild swelling (≤ 5 cm in diameter) at the injection site resolving within 2 days was commonly observed in field studies."

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 there is a negligible risk to the environment associated with use of the vaccine.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

All experiments conducted with Fencovis in laboratory and field conditions were designed to meet the requirements of the relevant veterinary legislation, including European Directive 2001/82/EC, as amended (2009/9/ES) and relevant European Pharmacopoeia monographs in force.

After vaccination of pregnant cows, efficacy of all antigens was proven by challenge of the target animals (born calves) with relevant challenge strains of bovine coronavirus, rotavirus and *E. coli*.

Efficacy studies have been performed with a vaccine batch with minimum antigen content produced according to the described production process.

Field studies have been performed with a representative vaccine batch produced according to the described production process.

Laboratory Trials

The efficacy of the product has been demonstrated in controlled laboratory studies in accordance with the relevant requirements using life heterologous challenge strains (a G6 BRV strain, a BCV strain and

a K99 E. coli strain) administered by oral route. The challenge infection for efficacy against neonatal colibacillosis was performed 12 hours after the calves were born, the challenge infections for efficacy against bovine rota- and coronavirus were performed at 7 days of age and for efficacy against coronavirus again at 14 days of age.

In each study,
ten cows were administered vaccine, five cows served as controls and received placebo. Subsequently, the newborn calves were fed for seven days with colostrum and milk from vaccinated cows or non-vaccinated control cows.
The signs of disease (diarrhoea) were noted every day in each calf and the severity was evaluated according to a specified scoring system. Faeces samples were taken daily from the day of challenge for the next seven days to determine the amount of excreted virus for bovine rotavirus and bovine coronavirus.
For bovine rotavirus and *E. coli,* all control calves showed moderate to severe diarrhoea following the challenge. No signs of disease were observed in animals fed with colostrum/milk derived from vaccinated cows. As no diarrhoea was observed in laboratory study in any animal of the vaccinated group, the proposed indication "prevent diarrhoea caused by bovine rotavirus and *E. coli*..." is acceptable.
For bovine coronavirus, a significant reduction in diarrhoea in calves fed with colostrum and milk from vaccinated cows compared to those fed with colostrum and milk from controls was recorded.
For bovine rotavirus and bovine coronavirus, the amount of excreted virus was significantly lower in animals fed with colostrum/milk from vaccinated cows than in the group of controls.

Accordingly, the active immunisation of pregnant heifers and cows was demonstrated to stimulate the development of antibodies against rotavirus, coronavirus and *E. coli* F5 (K99) adhesin and to increase the level of passive immunisation of calves against neonatal diarrhoea caused by rotavirus, coronavirus and *E. coli* F5 (K99) adhesin.
In calves fed with colostrum and milk from vaccinated cows for at least 7 days, these antibodies have been demonstrated to:

- prevent neonatal diarrhoea caused by bovine rotavirus and *E. coli* expressing F5 (K99) adhesin,
- reduce the incidence and severity of neonatal diarrhoea caused by bovine coronavirus,
- reduce faecal shedding of virus in calves infected with bovine rotavirus and bovine coronavirus.

Onset of immunity:
In calves fed with colostrum from vaccinated heifers or cows passive immunity commences with colostrum feeding and is dependent on calves receiving sufficient colostrum after birth.

Duration of immunity:
Calves fed with colostrum and milk from vaccinated dams for the first week of life are protected against bovine rotavirus for 7 days and against bovine coronavirus for 14 days.
The duration of immunity against infections caused by *E. coli* expressing F5 (K99) adhesin was not studied since such disease is usually observed in calves less than 3 days of age and susceptibility to enterotoxigenic *E. coli* is age dependent.

Field Trials

A combined safety and efficacy field trial was performed on target animals.

The trial enrolled cows/heifers 12-3 weeks before the expected date of calving and their newborn calves from two sites. A total number of 60 pregnant cows/heifers were selected on two farms. Animals were randomly allocated to vaccine or control group, so that there were 20 vaccinated and 10 control animals, housed in a single building, on each farm. Cows/heifers of the vaccine group received 2 ml of Fencovis intramuscularly on day 0, control animals were not vaccinated. Their calves (40 from the vaccinated and 17 from the control mothers) were included in the follow up of the study.

The efficacy of the vaccine was assessed:

- In cows by comparing the serum antibody response to the three vaccine antigens in vaccinated and control animals, using blood samples collected 7 days before vaccine administration and on the day of calving
- In colostrum and milk, by monitoring the kinetics of the antibodies against the three vaccine antigens in both vaccinates and controls.
- In calves, after being fed with the colostrum and milk from their mothers (vaccinates and controls), from the day of birth until 14 days later. Passively transferred antibodies to the three vaccine antigens in serum of calves were compared between groups, using samples collected on the day after birth, and then 5 and 14 days after birth.

For all three antigens, on both farms, antibody concentrations at the time of inclusion (D-7) were not significantly different between vaccinates and controls.
After vaccination, antibody titres raised significantly in vaccinates and on the day of calving, antibody titres were significantly higher in vaccinates than in control animals.
In cow colostrum/milk, the antibody kinetics followed a clear pattern of maximum level on day 1, declining rapidly to day 4 or 5 (when colostrum becomes milk), and then more slowly to day 14.

In all cases and at each time point the mean antibody concentrations were higher in vaccinates than in controls.

The calves which received colostrum and milk from vaccinates, showed distinctly higher antibody concentrations than calves fed with colostrum and milk from control mothers. Calves from vaccinated group showed higher serum antibody concentrations declining slowly until day 14 while the concentrations remained low and relatively stable in calves from control mothers.

The serological results of the tested groups (dam's serology, antibodies in colostrum/milk, calves' serology) were evaluated statistically. Altogether, these results confirm that administration of the vaccine to pregnant cows in the period of 12-3 weeks before expected delivery induced a significantly higher level of specific antibodies to bovine rotavirus, bovine coronavirus and *E. coli* F5 in calves receiving colostrum and milk from vaccinated mothers, compared with calves receiving colostrum and milk from unvaccinated mothers.

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.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).