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PUBLICLY AVAILABLE ASSESSMENT REPORT

FOR THE IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

Bovilis Rotavec Corona

Emulsion for Injection for Cattle

PRODUCT SUMMARY

EU procedure number	DE/V/0276/001/MR
Name and pharmaceutical form	Bovilis Rotavec Corona Emulsion for Injection for cattle
Applicant	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer Netherlands
Active substances	Inactivated bovine rotavirus, strain UK-Compton, serotype G6 P5 Inactivated bovine coronavirus, strain Mebus Inactivated E. Coli strain CN7985, serotype O101:K99:F41
ATC vetcode	QI02AL01
Target species	Cattle (pregnant cows and heifers)
Indication for use	For the active immunisation of pregnant cows and heifers to raise antibodies against *E. coli* adhesins F5 (K99) and F41, rotavirus and coronavirus. While calves are fed colostrum from vaccinated cows during the first two to four weeks of life, these antibodies have been demonstrated to: - reduce the severity of diarrhoea caused by *E. coli* F5(K99) and F41 - reduce the incidence of scours caused by rotavirus - reduce the shedding of virus by calves infected with rotavirus or coronavirus. <u>Onset of Immunity:</u> Passive protection against all active substances will commence from the start of colostrum feeding. <u>Duration of Immunity:</u> In calves artificially fed with pooled colostrum, protection will continue until colostrum feeding ceases. In naturally suckled calves, protection against rotavirus will persist for at least 7 days and against coronavirus for at least 14 days.

Product name	Application number
Applicant	MRP/DCP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this immunological veterinary medicinal product (IVMP) are available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application	Mutual recognition application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	16th March 2000.
Date immunological veterinary medicinal product first authorised in the Reference Member State (MRP only)	12th April 1999.
Concerned Member States (CMS) for original procedure	Austria, Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain
Date of completion of the subsequent use procedure – E001	3rd April 2008.
CMS for subsequent use procedure – E001	Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia, Slovenia, Sweden
Date of completion of the RMS change procedure	21st December 2017
Date of completion of the subsequent use procedure – E002	10th April 2018
CMS for subsequent use procedure – E002	Finland
Date of completion of the subsequent use procedure – E003	22nd January 2020
CMS for subsequent use procedure – E003	Norway

1. SCIENTIFIC OVERVIEW

The product is an inactivated adjuvanted vaccine emulsion for injection, for intramuscular administration to pregnant cows and heifers, in order to raise antibodies against the *Escherichia coli* adhesion F5 (K99) and F41 antigens, and specific coronavirus and rotavirus strains. Calves fed colostrum from vaccinated animals show a reduced incidence of scour caused by rotavirus, reduced viral shedding of coronavirus or rotavirus, and reduction of the severity of diarrhoea caused by *E. coli* F5 (K99) and F41. In naturally suckled calves, rotaviral protection persists for at least 7 days, and persists against coronavirus for at least 14 days.

The vaccine is manufactured and controlled using validated methods and tests that ensure the consistency of the IVMP released on the market.

The IVMP can be safely used in the target species.

The IVMP is also 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 IVMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

Bovilis Rotavec Corona is a liquid inactivated vaccine used to vaccinate heifers and pregnant cows to provide passive protection to new-born calves against *E. coli*, bovine rotavirus (BRV) and bovine coronavirus (BCV). The adjuvants are light mineral oil and aluminium hydroxide, and the excipients are thiomersal, formaldehyde, sodium thiosulphate and sodium chloride. The finished product is a water-in-oil emulsion, with the antigens adsorbed onto aluminium contained in the aqueous phase.

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

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvants, vaccine strains, inactivating agent and the presence of preservative are justified. The selection of the manufacturing process of the active substances and the finished product is explained.

Characterisation of the active substances including the determination of biological properties, biological activity, immunochemical properties, purity and impurities of the active substances is provided in order to allow suitable specifications to be established.

2.B. Description of the manufacturing method

The IVMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the IVMP are provided in accordance with the relevant European guidelines. The product is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

The inactivation processes and the detection limits of the control of the individual inactivation procedure are correctly validated.

2.C. Production and control of starting materials

The active substances are inactivated bovine rotavirus, bovine coronavirus and the *E. coli* F5 (K99) and F41 adhesion antigens. The active substances are manufactured in accordance with the principles of good manufacturing practice. The active substance specifications are considered adequate to control the quality of the material.

The master and working seeds were produced according to the seed lot system as described in the relevant guideline.

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

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately assessed for the absence of extraneous agents according to the relevant guidelines and any deviation is adequately justified.

Starting materials of non-biological origin used in production comply with appropriate control data (Ph. Eur. Monographs) or in-house specifications.

Batch analytical data demonstrating compliance with the determined specifications are provided.

2.D. Control tests during the manufacturing process

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

In-process control tests are carried out on intermediate stages of manufacture in order to verify the consistency of the manufacturing process and the final IVMP.

A specification was set for each intermediate and the analytical methods are described and validated, if applicable.

2.E. Control tests on the finished product

For all tests, a short description of the techniques for analysing the finished product is provided. The tests and their specifications and limits are justified and are considered appropriate to adequately control the quality of the IVMP.

Satisfactory validation data for each analytical methods are provided, if appropriate.

The tests performed on the final product conform to the relevant requirements and monographs, if applicable; any deviation from these requirements is justified.

Batch analytical data from the proposed production site are provided demonstrating compliance with the determined specification.

2.F. Batch-to-batch consistency

The demonstration of the batch-to-batch consistency is based on the results of three final product batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

Full protocols of the three consecutive batches of the final product are provided.

2.G. Stability tests

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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 of 2 years when stored under the approved conditions.

The in-use shelf-life of 28 days after first broaching of the vaccine container is supported by the data provided. The recommendations in the product leaflet should be followed by the user.

2.H. Other information

Store and transport refrigerated (2 °C – 8 °C).
Do not freeze.
Protect from light.

Particularly strict precautions should be taken against contamination of the vaccine.

The use of a multi-dose syringe is recommended to avoid excessive broaching of the stopper.

Once a vial is broached for the first time it may be used once more during the next 28 days and then discarded immediately after that use.

The content of the vial should not be used beyond 28 days after first broaching.

After broaching and first use, store upright and refrigerated (2 °C – 8 °C) until the next vaccination event.

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. General requirements

The safety of the IVMP when administered to the target species, the potential harmful effects (residues in IVMP, substance in foodstuff), the potential serious risk for human beings during product administration and to the environment are adequately described.

3.B. Pre-clinical studies

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal was demonstrated. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Effects on reproductive performance were examined. The product may be used during pregnancy. The vaccine is inactivated. An appropriate warning in the SPC is included barring the user from mixing the products with any other medicinal product.

3.C. Clinical trials

Appropriate field studies were conducted.

3.D. Environmental Risk Assessment

The applicant provided an appropriate risk assessment in compliance with the relevant guideline, which showed that no further assessment is required. The assessment concluded that all hazards identified have a negligible likelihood and therefore the estimation of the risk of these hazards is effectively zero.

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

3.E. Assessment required for veterinary medicinal products containing or consisting of genetically modified organisms

Not applicable.

4. EFFICACY DOCUMENTATION

4.A. General requirements

The efficacy of the IVMP when administered to the target species are adequately described.

4.B. Pre-Clinical Studies

The efficacy of the product has been demonstrated in laboratory studies under well-controlled conditions in accordance with the relevant requirements.

Suitable dose confirmation studies were provided.

4.C. Clinical trials

Efficacy of vaccination was also demonstrated under field conditions. Suitable studies were provided.

5. 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, safety and efficacy of the product for the target species pregnant cows and heifers, humans and the environment is acceptable when Bovilis Rotavec Corona is used in accordance with the Summary of Product Characteristics.

POST-AUTHORISATION PROCEDURES

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/labelling/package leaflet is/are available in the Union Product Database (UPD).

This section contains information on significant changes agreed after the original procedure, which are important for the quality, safety or efficacy of the product.

Sequence of significant variations

Summary of change (Application number)	**Approval date**
Initial MRP in AT, BE, DE, ES, FR, GR, IE, IT, LU, NL and PT (UK/V/0138/001)	March 2000
Changes to shelf life (withdrawn) (UK/V/0138/001/V01)	n.a.
Changes to pH value (UK/V/0138/001/V02)	November 2000
Changes to minimizing TSE risk (UK/V/0138/001/W01)	July 2002
Changes to lower end of shelf life potency release limit for coronavirus (UK/V/0138/001/W03)	November 2002
Changes to add alternative source of insulin (UK/V/0138/001/V04)	May 2003
Changes to add alternative source of meat peptone (UK/V/0138/001/V05)	May 2003
Changes to add three suppliers of foetal calf serum (UK/V/0138/001/V06)	May 2003
Changes to increase the shelf life to 24 months (UK/V/0138/001/IB/001)	June 2004
Renewal procedure (UK/V/0138/001/N001)	November 2004
Changes to add 2 ml presentation (10 x 1 dose) (UK/V/0138/001/IB/002)	April 2006
Changes to oleic acid of animal origin to vegetable origin; Changes to Montanide ISA70 to Montanide ISA70VG (UK/V/0138/001/IB/003)	September 2006
RUP, now subsequent use procedure – E001 to add the CMS: BG, CY, CZ, DK, EE, HU, LT, LV, MT, PL, RO, SK, SI and SE (UK/V/0138/001/E/001)	April 2008

Change of the MAH in FR (UK/V/0138/001/IA/004)	August 2009
Renewal procedure (UK/V/0138/001/R/002)	August 2010
Change to pH value (UK/V/0138/001/V02)	November 2010
Change to introduce a new Pharmacovigilance system (UK/V/0138/001/IB/005)	October 2010
Changes to the name of the manufacturer of the active substance (now: Burgwedel Biotech GmbH) (UK/V/0138/001/IA/006/G)	April 2011
Changes to name/address of the MAH in PT (UK/V/0138/001/IA/007/G)	August 2011
Changes to introduce recombinant human insulin for the growth of CHO cells (minimizing TSE risk) (UK/V/0138/001/IB/008)	November 2011
Changes to Target Animal Batch Safety Test (TABST), notification of the omission of TABST	March 2013
Change to down scale Thiomersal specification to 0.016 mg/ml (UK/V/0138/001/II/009)	January 2014
Change to delete Al^{3+} test during finished product stability testing (UK/V/0138/001/IA/010) – refused and re-submitted as 013	n.a.
(UK/V/0138/001/IB/011) – withdrawn and re-classification to type II variation and re-submitted as 012	n.a.
Changes to optimize in-process coronavirus antigen ELISA (UK/V/0138/001/II/012)	September 2014
Changes to quantitative Al^{3+}-testing during finished product stability studies (UK/V/0138/001/IA/013)	October 2014
Worksharing procedure UK/V/xxxx/IA/070/G to update DDPS (UK/V/0138/001/IA/014/G)	December 2014
Changes to add manufacturer of an active substance (here; Intervet International GmbH, for coronavirus antigen) (UK/V/0138/001/II/015/G)	May 2015
Changes to specifications of the coronavirus antigen ELISA (UK/V/0138/001/IB/016) – refused	n.a.
Worksharing procedure UK/V/xxxx/IA/116/G to update DDPS (UK/V/0138/001/IB/017/G)	November 2016
RMS transfer from UK to DE in preparation of BREXIT (DE/V/0276/001)	December 2017
RUP, now subsequent use procedure (New Vet. Regulation 2022) – E002 administrative RUP to add the CMS FI (DE/V/0276/001/E/002)	April 2018

Changes to update the dossier after fulfilment of commitment (filtration step) (DE/V/0276/001/IB/018)	May 2018
Worksharing procedure ES/V/xxxx/IA/031/G to update DDPS (DE/V/0276/001/IA/019/G)	October 2018
Worksharing procedure DE/V/xxxx/WS/063 to: - change the invented name: “Bovilis Rotavec Corona” - indroduction of an antigen ELISA for the BRV antigen (IPC ELISA) - change to an *in vitro* potency assay for the BRV component (BRV IVP ELISA) - addition of multi-dose presentations in PET containers - addition of a 100 ml (50 dose) presentation - extension of the in-use shelf life from 8 hours to 28 days - additional editorial changes (DE/V/0276/001/WS/020)	September 2019
RUP, now subsequent use procedure (New Vet. Regulation 2022) – E003 administrative RUP to add the CMS NO (DE/V/0276/001/E/003)	January 2020
Supergrouping with IE as RMS IE/V/xxxx/IA/166/G to change the MAH name in UK (DE/V/0276/001/IA/021/G)	April 2018
Worksharing procedure DE/V/xxxx/WS/073 to: - add new active substance manufacturer Intervet International BV (Boxmeer) for *E. coli* (K99), BRV and BCV antigens - add TSE CEPS for relevant materials used in Boxmeer, NL - reduce the inactivation time for *E. coli* (K99) and BRV antigens - add alternative plastic containers for interim storage of *E. coli* (K99) antigens - delete two in process control tests for *the E. coli* (K99) antigen (purity test at step A04 and sterility testing on the inactivated harvest (steps A09-10)). - introduce a virus titration as in process control test for the BCV antigen instead of an antigen content test (fulfilment of a commitment from a previous variation UK/V/0138/001/IB/016) - additional editorial changes (DE/V/0276/001/WS/022)	September 2021
Worksharing procedure DE/V/xxxx/WS/078 to: - add Intervet International B.V. (Boxmeer, NL) for in process quality control testing for the *E. coli* (K99), BRV and BCV antigens - replacement of current agglutination assays for identity and antigen content for *E. coli* (K99) with an *E. coli* (K99) antigen content ELISA - change to an *in vitro* potency assay for the *E. coli* (K99) component (*E. coli* IVP ELISA) - change to an *in vitro* potency assay for the BCV component (BCV IVP ELISA) - add additional information on the characterization of the *E. coli* strain in the vaccine. The *E. coli* antigen strain will be	September 2022

specified as follows: *E. coli* strain CN7985, serotype O101:K99:F41. (DE/V/0276/001/WS/023)	