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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

RISPOVAL 2 BRSV + PI3 LYOPHILISATE AND SUSPENSION FOR SUSPENSION FOR INJECTION FOR CATTLE

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0420/001/DC
Name, strength and pharmaceutical form	RISPOVAL 2 BRSV + Pi3 Lyophilisate and suspension for suspension for injection for cattle
Applicant	ZOETIS
Active substance(s)	attenuated bovine parainfluenza 3 virus (Pi3V) strain RLB 103 attenuated bovine respiratory syncytial virus (BRSV) strain 375
ATC Vetcode	QI02AD07
Target species	cattle
Indication for use	Active immunisation of calves from 12 weeks of age to : - Reduce virus excretion caused by bovine Pi3 virus infection - Reduce virus excretion caused by BRSV infection

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

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	21/10/2020
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Czech Republic, Germany, Estonia, Spain, Croatia, Hungary, Ireland, Lithuania, Lettonia, Luxemburg, The Netherlands, Portugal, Slovenia, Slovakia, United Kingdom

I. SCIENTIFIC OVERVIEW

RISPOVAL 2 is a bivalent vaccine for bovine use presented as a lyophilisate fraction containing live BRS and Pi3 viruses to be reconstituted with a liquid fraction containing aluminium hydroxide. The vaccine is to be used in cattle from 12 weeks of age (2 doses 3-4 weeks apart via intramuscular route) to reduce virus excretion of BRS and Pi3 viruses.

The 2 active substances contained in this vaccine have been licensed in other combination vaccines such as RISPOVAL 4 or RISPOVAL 3 from which this vaccine is derived.

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 minor 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. Composition

The product is constituted of a freeze-dried fraction containing the following live attenuated ingredients :

Ingredients	Quantity per dose
Active ingredient Bovine Parainfluenza 3 virus (Pi3V), modified live strain RLB 103 Bovine Respiratory Syncytial Virus (BRSV), modified live strain 375	 $10^{5.0}$ – $10^{8.6}$ $CCID_{50}$ (*) $10^{5.0}$ – $10^{7.2}$ $CCID_{50}$ (*)
Excipient(s) *Lactose Monohydrate* *Potassium hydrogen phosphate* *Dipotassium phosphate* *Monopotassium L-glutamate* *Water, purified* *Gelatin* *Casein hydrolysate solution* *HALS medium*	 Qsp 1 dose

(* CCID50 = Cell Culture Infectious Dose 50%)

and a liquid fraction :

Ingredients	Quantity per dose
Aluminium hydroxide gel HALS medium	0.8 ml Qsp 4 ml

The lyophilised fraction is to be reconstituted with the liquid one before vaccination.

The two fractions are filled in glass vials closed with chlorobutyl rubber (liquid fraction) or bromobutyl rubber (freeze-dried fraction) stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains, the production process, the adjuvant and the formulation are justified.

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.

C. Control of Starting Materials

The active substances - bovine respiratory syncytial virus and bovine parainfluenza virus type 3 - are active substances described in the European Pharmacopoeia. They are manufactured in accordance with the principles of good manufacturing practice.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline. The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with the specifications have been provided.

Starting materials of non-biological origin used in production comply with relevant European 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 ; any deviation was adequately justified.

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 and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product are conform to the relevant requirements. The tests include in particular

Lyophilisate :
- description
- identification and titration of the active ingredients,
- bacterial, fungal and mycoplasmic sterility according to Ph Eur,
- absence of extraneous agents,
- residual humidity

Liquid fraction
- description,
- sterility,
- aluminium content,

- pH

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. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the freeze-dried and liquid fraction throughout shelf life when stored under the approved conditions : 24 months at 2-8°C.

The reconstituted vaccine shall be used immediately after reconstitution.

III. SAFETY ASSESSMENT

Vaccine batches used in the safety studies are representative of the production process. In line with the guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (EMA/CVMP/IWP/594618/2010), allowing the use of multivalent data in support of a lesser-valent product, the safety of Rispoval 2 is demonstrated by studies conducted with the multivalent vaccine Rispoval 4. Although these studies are quite old, these safety data together with the large amount of field experience obtained from the more valent vaccines (RISPOVAL 3 and RISPOVAL 4) support the safety of the Rispoval 2 fall-out vaccine.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in healthy conventional calves. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. Transient and mild hyperthermia and local inflammation reactions which may be commonly observed after vaccination have been adequately described in the SPC.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals and the viruses included in the vaccine are not expected to be associated with any pathological effects in the reproductive tract.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny.

For each live strain included in the vaccine:

Specific studies were carried out which allow to confirm absence of spread, dissemination, or reversion to virulence of the vaccine virus strains. Both viruses are not capable of either recombination or reassortment.

The adjuvant and excipients used are not falling in the scope of MRL regulation 470/2009 or are included in table 1 of the MRL regulation 37/2010 without any MRL being required. Based on this information, no withdrawal period is proposed.

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

Field studies

A field study is performed with a parent more valent vaccine. Vaccination of more than 1000 calves from 4 months of age (with around 100 animals younger than 4 weeks) of mixed breeds in 20 conventional farms in France did not reveal other adverse vaccine reactions than those described in the SPC consisting mostly of slight hyperthermia in less than 2% of vaccinated animals.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

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)

Vaccine batches used in the efficacy studies are representative of the production process. In line with the approach described in the guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (EMA/CVMP/IWP/594618/2010), most studies provided have been conducted using the multivalent Rispoval 4 vaccine. Although these studies are quite old, these data support the efficacy of the fall-out Rispoval 2 vaccine. To confirm the absence of potential interactions of the BoHV-1 and/or BVDV strains on the induction of protection against BRSV and Pi3V, the applicant conducted 2 Onset of Immunity studies with Rispoval 2. In these studies, efficacy of Rispoval 2 against BRSV and Pi3V was shown by challenge and confirmed that the immunological response induced by Rispoval 2 is not compromised by the removal of BoHV-1 and BVDV (as contained in Rispoval 4).

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies.

Onset of immunity :

animals	vaccine	challenge	efficacy	comments
Seronegative calves 15 vaccinated / 15 controls	RISPOVAL 4 2 doses 3 weeks apart	3 weeks after vaccination Virulent BRSV strain	Significant reduction of virus excretion titre and reduction of virus excretion duration	supportive study conducted in the past with RISPOVAL 4 vaccine
Seronegative calves 13 vaccinates / 13 controls	RISPOVAL 2 2 doses 3 weeks apart	3 weeks after vaccination Virulent BRSV strain	Significant reduction of clinical signs and virus excretion (titre and duration)	Conform to EP monograph support claims and onset of immunity of Rispoval 2
Calves 12 vaccinated / 13 controls	RISPOVAL 4 2 doses 3 weeks apart	3 weeks after vaccination Virulent Pi3V strain	Significant reduction of clinical signs. .Significant reduction in Pi3V excretion (titre) and reduction in duration.	supportive study conducted in the past with RISPOVAL 4 vaccine
Calves with low levels of antibodies 16 vaccinates / 16 controls	RISPOVAL 2 2 doses 3 weeks apart	3 weeks after vaccination Virulent Pi3V strain	Significant reduction of virus excretion (titre and duration). Challenge strain did not induce clear clinical signs.	Conform to EP monograph support claims and onset of immunity of Rispoval 2

Duration of immunity

Calves seronegative or with low levels of antibodies 20 vaccinates / 20 controls	RISPOVAL 4 2 doses 3 weeks apart	12 months after vaccination Virulent BRSV strain (10 vaccinates / 10 controls) or virulent Pi3V strain (10 vaccinates / 10 controls)	Significant reduction of BRSV excretion (duration) Circulation of a Pi3 wild-type virus interfering with the study	study conducted in the past with RISPOVAL 4 vaccine Supporting the duration of immunity for BRSV
Calves colostrum fed	RISPOVAL 4 2 doses 3 weeks apart	6 months after vaccination	Circulation of field infections	study conducted in the past not

16 vaccinates / 16 controls		Virulent BRSV strain (8 vaccines / 8 controls) or virulent Pi3 strain (8 vaccinates / 8 controls)	with wild-type BRSV & Pi3V interfering with the study	conclusive and provided for information
Calves colostrum deprived and seronegative 14 vaccinates / 15 controls	RISPOVAL 4 2 doses 3 weeks apart	6 months after vaccination Virulent Pi3 virus strain	Circulation of a wild-type Pi3V interfering with the study	study conducted in the past not conclusive and provided for information

Field Trials

The applicant has conducted a field study with multivalent vaccine RISPOVAL 4 in 20 conventional farms including 478 vaccinates and 480 control calves of minimum 4 months old. This study did not bring any additional information on the efficacy of the vaccine.

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 veterinary Heads of Agencies website (www.HEVRA.org).

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