Institute for State Control of Veterinary Biologicals and Medicines
Ústav pro státní kontrolu veterinárních biopreparátů a léčiv

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

BOVALTO Respi 4 suspension for injection for cattle

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0129/001/MR
Name, strength and pharmaceutical form	**BOVALTO Respi 4** **suspension for injection for cattle**
Applicant	MERIAL, 29 avenue Tony Garnier, 69007 Lyon, France
Active substance(s)	Inactivated bovine respiratory syncytial virus, strain BIO-24 Inactivated bovine parainfluenza 3 virus, strain BIO-23 Inactivated bovine viral diarrhoea virus, strain BIO-25 Inactivated *Mannheimia haemolytica*, serotype A1 strain DSM 5283
ATCvetcode	QI02AL
Target species	Cattle
Indication for use	For active immunisation of cattle in the absence of maternally derived antibodies against: - parainfluenza 3 virus, to reduce virus excretion due to infection - bovine respiratory syncytial virus, to reduce virus excretion due to infection - bovine viral diarrhoea virus, to reduce virus excretion due to infection - *Mannheimia haemolytica* serotype A1, to reduce clinical signs and lung lesions.

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	Mutual Recognition application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21/10/2015
Date product first authorised in the Reference Member State (MRP only)	29/05/2015
Concerned Member States for original procedure	AT,BE,DE,EL,ES,FR,IE,LU,MT, PL,PT,RO ,UK

I. SCIENTIFIC OVERVIEW

The vaccine Bovalto Respi 4 suspension for injection for cattle is an inactivated vaccine containing bovine respiratory syncytial virus, bovine parainfluenza 3 virus, bovine viral diarrhea virus and *Mannheimia haemolytica* as antigens, aluminium hydroxide, quillaja saponin (Quil A), thiomersal, formaldehyde and saline.

Onset of immunity (demonstrated by challenge): 3 weeks after primary vaccination
Duration of immunity (demonstrated by challenge): 6 months after primary vaccination

The recommended vaccination scheme is:
Primary vaccination
Calves from non-immune dams: 2 injections 3 weeks apart from 2 weeks of age
Where the immune status of the dam is unknown the vaccine scheme should be adapted at the discretion of the veterinarian.
Revaccination
Administer a single dose 6 months after completion of the primary vaccination scheme.
The revaccination was demonstrated by measurement of the serological response. The efficacy of the revaccination has not been assessed by challenge.

Dosage – 2 ml administered subcutaneously.

The withdrawal period is zero days.

Stability data, which support the proposed shelf-life of 2 years in glass vials and 15 months in plastic vials, have been provided.

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 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

One dose (2 ml) contains:

Active substances:

Inactivated bovine respiratory syncytial virus, strain BIO-24	RP ≥ 1*
Inactivated bovine parainfluenza 3 virus, strain BIO-23	RP ≥ 1*
Inactivated bovine viral diarrhoea virus, strain BIO-25	RP ≥ 1*
Inactivated *Mannheimia haemolytica*, serotype A1 strain DSM 5283	RP ≥ 1*

*) Relative potency (RP) 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	8.0 mg
Quillaja saponin (Quil A)	0.4 mg
Excipients:	
Thiomersal	0.2 mg
Formaldehyde	1.0 mg at most

Container/closure system:

Type I glass bottle of 10 ml with chlorobutyl elastomer closure (5 doses)
Type II glass bottle of 50 or 100 mL with chlorobutyl elastomer closure (25 or 50 doses)
Translucent plastic bottle of 10, 50 or 100 mL with chlorobutyl elastomer closure (5, 25 or 50 doses)

Box of 1 bottle of 5 doses (10 ml)
Box of 10 bottles of 5 doses (10 x 10 ml)
Box of 1 bottle of 25 doses (50 ml)
Box of 1 bottle of 50 doses (100 ml)

The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strains, of the vaccine composition, adjuvants, inactivating agent, preservative, of the dose volume and vaccination schedule 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 from 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 indicated pharmacopoeia monographs.

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

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.

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.

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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. Relevant validations are provided.

The tests include in particular:

- appearance
- usable volume
- sterility

- inactivation test*****
- potency and identity
- pH value
- bacterial endotoxins assay*
- aluminium oxide assay
- formaldehyde assay
- thiomersal assay
- airtightness

* The test is carried out as the in-process control during production of antigens

For the *Mannheimia haemolytica* component, the potency of both the bacterin and leucotoxoid fraction is checked in guinea pigs.

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F. Batch to batch consistency

The consistency of production has been demonstrated and the results of 4 consecutive runs, conforming to the specifications, are provided.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances (for 6 months for *Mannheimia haemolytica* bacterin and 12 months for BVD, PI-3 and BRSV viral antigens) when stored under the approved conditions (2-8 °C for *Mannheimia haemolytica and* – 20 °C or lower for viral antigens).
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 in the glass vials and 15 months in plastic vials) 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.

III. SAFETY ASSESSMENT

The vaccine is recommended for cattle (for calves from 2 weeks of age) for 2 injections subcutaneous administration at an interval of 3 weeks.

Safety clinical findings have been based on the recommended vaccination scheme.

Laboratory trials

Safety studies have been performed with a vaccine batch (containing maximum content of all antigens) produced according the described production process.

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in controlled laboratory studies which in total included 20 vaccinates animals (2-week-old calves). The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The safety studies demonstrate that the administration of one dose, an overdose 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:

Following vaccination a localised swelling may be very commonly observed at the injection site. This swelling could reach up to 7 cm in diameter, and usually progressively reduces and disappears within 6 weeks after vaccination.
Commonly, there may be a transient slight increase in body temperature which was higher after the second injection (1.5°C at most) lasting up to 3 days after vaccination.
Anaphylactic-type reactions may very rarely occur after vaccination. In such cases, appropriate symptomatic treatment should be administered.

Vaccine is not intended for administration to pregnant and / or lactating animals. Therefore, no specific studies were performed. The proposed text of SPC reflects this claim.

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 gel, Quil A, thiomersal, used as a preservative and formaldehyde, used as an inactivating agent. All the excipients included in the final product are recorded in Annex II to EEC Council Regulation No. 2377/90 as the substances for which MRLs do not apply. 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

Combined safety and efficacy field trial was performed on target animals.

The clinical evaluation was performed within the private practices of two veterinary doctors, on three farms in total. Of each herd, the total number of 40 animals (20 calves and 20 pregnant cows) were included in the clinical evaluation, of which a half as a minimum was subject to blood taking for the purpose of monitoring of their serological response.

A batch of the vaccine, containing average titres of the antigens, produced by the method described in the marketing authorisation documentation was used in the study. Animals were vaccinated according to the vaccination schedule recommended in Summary of Product Characteristics. Within the safety evaluation, the animals were observed for 14 days after the last application of the vaccine to detect a possible occurrence of local and general reactions. The body temperature was monitored 3 days before vaccination, during vaccination and 4 days following vaccination.

The clinical trial was supplemented on the basis of comments of the national authority within the registration procedure.

The European Pharmacopoeia monograph "*Mannheimia vaccine (inactivated) for cattle*" requires to evaluate, within a field study, the safety in vaccinated calves in 3 groups of 20 calves and 10 control animals in 3 different herds. An additional study was conducted at two

locations. The study was used to monitor the safety of administration of the tested vaccine so as to meet the requirement of the European Pharmacopoeia monograph.

The results of field studies are in compliance with Ph. Eur. Monograph 1944, no animal showed notable signs of disease or died from causes attributable to the vaccine; the average body temperature increase for all animals did not exceed 1.5 °C; and no animal showed a rise in body temperature greater than 2 °C.

The results from field trials reflect those observed in laboratory trials.

Ecotoxicity

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

The conclusions of the environmental risk assessment as presented by the applicant, that there is a negligible risk to the environment associated with use of the vaccine, are accepted. The applicant has included the standard disposal statement for inactivated vaccines on the product literature and this is considered acceptable.

IV. EFFICACY

All experiments conducted with Bovalto Respi 4 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. The efficacy of the product has been demonstrated in laboratory challenge studies on the target species in animals at the minimum age recommended for vaccination (2 weeks). The batch of minimum declared potency used in the trials was manufactured using the procedure described in the marketing authorisation documentation.

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements.

Onset of immunity

The laboratory tests of efficacy were performed in accordance with the pharmacopoeial monographs no. 1176 (Vaccinum parainfluenzae viri bovini vivum cryodesiccatum); 1177 (Vaccinum viri syncytialis meatus spiritus bovini vivum cryodesiccatum); 1944 (Vaccinum mannheimiae inactivatum ad bovinas).
The BVD component was not tested according to the pharmacopoeial monograph (by challenge test in heifers) as the vaccine in this composition is not designed to protect the foetus during pregnancy, but only as a part of polyvalent vaccine against respiratory diseases.
Challenge tests of efficacy were performed in laboratory conditions 3 weeks after immunization with all vaccine components.
Control non-vaccinated animals were included in all challenge tests within the experiment.
Clinical status of all experimental animals was monitored daily during the challenge tests and their body temperature was measured. Moreover, the presence of challenge virus was observed in nasal swabs in case of challenge tests with the parainfluenza virus, BRSV and the BVD virus.

<u>Challenge models - Verification of infection dose</u>

The selected infection dose was verified by challenge test on sensitive animals.

After the virus applications, very moderate clinical symptoms of disease were observed, the virus excretion was recorded from day 3 to day 7 after infection. The serological examination proved the creation of specific virus neutralization antibodies related to the application of challenge virus.

After application of the challenge strain of *Mannheimia haemolytica*, moderate clinical symptoms of disease were recorded in the form of apathy, cough and nasal discharge or dyspnoea. Simultaneously, animals manifested a positive culture finding in pulmonary samples.

Onset of immunity

The challenge tests performed in sensitive animals proved the satisfactory efficacy of the vaccine Bovalto Respi 4 against the infection with PI-3, BRSV, BVD viruses. The statistical evaluation of the acquired data proved a significant difference in the duration of virus excretion and the quantity of excreted virus between the vaccinated groups and the non-vaccinated control groups.

The satisfactory efficacy of the vaccine against the infection with a field isolate of *Mannheimia haemolytica*, was assessed by comparing the clinical symptoms of the disease, total lung scores and infection agent re-isolation following challenge in group vaccinated as compared with the control group of unvaccinated animals. The statistical evaluation of the acquired data proved a significant difference in the pulmonary score and clinical signs between the vaccinated group and the non-vaccinated control group.

Duration of immunity

Challenge tests of efficacy were performed in sensitive animals 6 months after the basic immunization

The statistical evaluation of the acquired data proved a significant difference in the duration of virus excretion and the quantity of excreted virus between the vaccinated groups and the non-vaccinated control groups for all virus components and a significant difference in the pulmonary score and clinical signs for *Mannheimia haemolytica.*

The following claimed indications for Bovalto Respi 4 are considered to be supported by the laboratory studies:

For active immunisation of cattle in the absence of maternally derived antibodies against:
- parainfluenza 3 virus, to reduce virus excretion due to infection
- bovine respiratory syncytial virus, to reduce virus excretion due to infection
- bovine viral diarrhoea virus, to reduce virus excretion due to infection
- Mannheimia haemolytica serotype A1, to reduce clinical signs and lung lesions.
Onset of immunity (demonstrated by challenge):
3 weeks after primary vaccination
Duration of immunity (demonstrated by challenge):
6 months after primary vaccination

Influence of Maternal antibodies on efficacy

The study on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals has not been carried out. The applicant submitted references to the potential impact of MDA in general based on literature data.

The recommended vaccination scheme is:

Primary vaccination

Calves from non-immune dams: 2 injections 3 weeks apart from 2 weeks of age
Where the immune status of the dam is unknown the vaccine scheme should be adapted at the discretion of the veterinarian.
Revaccination
Administer a single dose 6 months after completion of the primary vaccination scheme.
The revaccination was demonstrated by measurement of the serological response. The efficacy of the revaccination has not been assessed by challenge.

Corresponding warning has been placed in the SPC in section 4.5:

Safety and efficacy studies were performed in sero-negative calves. The efficacy of the vaccination has not been demonstrated in presence of antibodies. The level of antibody response may be reduced by the presence of maternal antibodies. In the presence of maternal antibodies, timing of initial vaccination of calves should be planned accordingly.

This is acceptable.

Field studies

Combined safety and efficacy field trial was performed on target animals.

Of each herd, the total number of 40 animals (20 calves and 20 pregnant cows) were included in the clinical evaluation, of which a half as a minimum was subject to blood taking for the purpose of monitoring of their serological response.
In herd no. 1, the calves were vaccinated from 2 to 4 weeks of age and the blood was taken from 10 calves. Simultaneously, a control group of calves, vaccinated with the registered vaccine of similar composition as the tested vaccine but without the BVD antigen was included in the serological monitoring.
In herds no. 2 and 3, a half of the calves (i.e. 10 pieces) were vaccinated from 2 weeks of age and the second half from 8 weeks of age. Five calves of each category of age were selected to monitor their serological response. In these herds, a control group of non-vaccinated calves was included in the monitoring and the blood was taken from these calves for serological examination in similar intervals as from the vaccinated calves.

The product efficacy was evaluated on the basis of serological monitoring and monitoring of incidence of respiratory disease symptoms in vaccinated calves.

The results obtained in this study support the findings obtained in the laboratory trials.

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.