MEB agency / Veterinary Medicinal Products Unit
The Netherlands

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bovilis INtranasal RSP Live

Created: November 2019

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0257/001/DC
Name, strength and pharmaceutical form	Bovilis INtranasal RSP Live, nasal spray, lyophilisate and solvent for suspension.
Applicant	Intervet International B.V. Wim de Körverstraat 35, 5831 AN P.O. Box 31, 5830 AA, Boxmeer The Netherlands.
Active substance(s)	Live bovine respiratory syncytial virus (BRSV) strain Jencine-2013. Live bovine parainfluenza virus type 3 (PI3), strain INT2-2013
ATC Vetcode	QI02AD07
Target species	Cattle
Indication for use	For active immunisation of calves from the age of 1 week old onwards to reduce clinical signs of respiratory disease and viral shedding from infection with BRSV and PI3. Onset of immunity: BRSV: 5 days PI3: 1 week Duration of immunity: 12 weeks

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).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full dossier application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17 April 2019
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK.

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

The product contains the active substances attenuated bovine respiratory syncytial virus strain Jencine-2013 (≥ 5.0 and ≤ 7.0 $\log_{10}$ $TCID_{50}$ per dose) and attenuated parainfluenza virus type 3 strain INT2-2013 (≥ 4.8 and ≤ 6.9 $\log_{10}$ $TCID_{50}$ per dose. The solvent for use with this vaccine is Unisolve (ingredients: sucrose, potassium dihydrogen phosphate, disodium phosphate dehydrate, sodium chloride and water for injections), which has previously been approved for use with other vaccines.

The vaccine is filled in hydrolytical Type I glass vials of 3, 10 and 20 ml for the 1, 5 and 10 dose presentation respectively. The 3 ml presentation of Unisolve is filled in type I glass vials and the 10 and 20 ml presentations of Unisolve are filled in type II glass vials. After filling, the vials of both the vaccine and the solvent are closed with a halogenobutyl rubber stopper and sealed with an aluminium cap.

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.

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

C. Control of Starting Materials

Starting materials of non-biological origin used in production of the vaccine and solvent comply with the relevant Ph. Eur. Monographs (and for pancreatic digest of casein with the relevant USP monograph).

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.

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

D. Control tests during production

The tests performed during production are described 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 conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular visual inspection of appearance, solubility, vacuum test, batch titre and identification of the active substances, purity and sterility tests and residual humidity. For the solvent Unisolve, tests for appearance, clarity, colour, filling volume, pH, determination of sucrose content, identity and sterility are performed on every batch. Tests for clarity, colour, pH, identity and sterility are performed in accordance with the respective Ph. Eur. Monographs. Sucrose content is determined by a validated HPLC method. Release requirements are provided.

The demonstration of the batch to batch consistency is based on the results of 4 consecutive batches of the final product produced according to the method described in the dossier, and 3 batches of the solvent. Other supportive data provided confirm the consistency of the production process.

F. Stability

The active substance is tested to ensure compliance with its specification immediately prior to its use in manufacture of the finished product.

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 when stored under the approved conditions.

The claim of a 6 hours stability after reconstitution is based on the demonstration of stability for two batches which were broached and stored for 6 hours at 15-25°C.
The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

G. Other information

Not applicable.

III. SAFETY ASSESSMENT

Under laboratory and field conditions the following aspects were addressed:

- Observations of local and systemic reactions after vaccination of an 10x maximum dose
- Dissemination, shedding and spreading of BRSV Jencine-2013
- Dissemination, shedding and spreading of PI3 INT2-2013
- The potential of BRSV Jencine-2013 to revert to virulence
- The potential of PI3 INT2-2013 to revert to virulence
- Observations of local and systemic reactions after vaccination of a single dose under field conditions
- Observations of local and systemic reactions after vaccination of a single dose under field conditions

The laboratory studies were conducted in compliance with the principles of Good Laboratory Practice (GLP) as specified by national and international legislation. The field studies were conducted in compliance with Good Clinical Practice (GCP).

Laboratory trials

The safety of the administration of an overdose in the target animal is demonstrated in one GLP overdose safety study and one supportive study. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. In the supportive study (near-maximum dose of the vaccine), 6 calves aged between 5 and 11 days were vaccinated intranasally with 6 ml of the vaccine containing 6.8 $\log_{10}$ $TCID_{50}$ BRSV and 6.7 $\log_{10}$ $TCID_{50}$ PI3. One animal remained unvaccinated as a control. In the overdose safety study, 5 calves aged between 4 and 7 days were vaccinated intranasally with 8 ml of the vaccine containing 8.0 $\log_{10}$ $TCID_{50}$ BRSV and 7.5 $\log_{10}$ $TCID_{50}$ PI3. Animals treated with 10x maximum dose of the vaccine showed mild upper and lower respiratory signs (mild nasal discharge) and a slight increase in the average rectal temperature, whereas in the supportive 1x maximum dose study only rectal temperatures in vaccinated individuals showed a small temporary increase. In a developmental laboratory efficacy study, a slight increase in the average rectal temperature between day 2 and day 5 was observed as well. The respiratory clinical signs and the temperature increase observed in the 10x maximum dose study are adequately captured in the SPC section 4.6.

No investigation of effect on reproductive performance was conducted because the vaccine is intended for use in young calves. The SPC includes the warning “Do not use during pregnancy and lactation.” in section 4.7.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal. The applicant investigated transcription of genes involved in the immune response in nasal brush samples of calves included in a vaccination-challenge study. It appears vaccination is associated with increased transcription of genes encoding receptors and cytokines involved in anti-viral innate immune responses, while no expression of cytokines involved in adverse reactions (such as fever) was demonstrated. Following vaccination a minimal down regulation of bacterial immune pathways occurred, which is in line with what would be expected in a vaccine intended to provide protection against viral pathogens.

Spreading, dissemination, shedding and the presence of residues was assessed for each vaccine virus separately. Dissemination of BRSV strain Jencine-2013 within animals was limited. The level of shedding was low, occurring only in nasal secretions between 2 and 12 days post inoculation. Spreading was not observed. Only limited residues of vaccine virus were found at the site of vaccination (RT-qPCR positive). For PI3 strain INT2-2013, the

vaccine virus disseminated in the body, mainly to the respiratory tract. Vaccinated calves shed the virus (nasal, ocular, urine, faeces) between 2 and 10 days post inoculation. The virus spread to sentinel animals (detection of virus and antibody response), and these animals also shed the virus. The warning sentence “Vaccinated calves may excrete the vaccine strains up to 12 days following vaccination. It is recommended to vaccinate all calves of in the herd.” mitigates the risks of dissemination and shedding of both vaccine viruses.

Reversion to virulence of the attenuated vaccine strains was evaluated for BRSV and PI3 separately. The results of these studies show no indication of reversion to virulence over five passages in seronegative (colostrum deprived) calves for PI3, while for BRSV it was shown that the virus is unable to be passaged in susceptible calves.

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

User Safety

As all components of the vaccine are considered safe, the risk of self-injection and skin exposure is negligible. Therefore no user safety warnings are included in section 4.5 of the SPC.

Residues

The active substances of this bivalent vaccine are live attenuated strains of BRSV and PI3. All excipients and the constituents of the excipients are either of biological origin or are included in Table 1 of Commission regulation No 37/2010. The vaccine does not contain any components in quantities that may pose a risk to human health, or require a maximum residual limit (MRL). Therefore, the withdrawal period is considered to be zero days, and a study of residues is not required.

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 for all identified hazards either the likelihood or the impact is considered negligible. Therefore the overall risk of the use of Bovilis INtranasal RSP Live to the environment is effectively zero. No warnings regarding the environment are therefore required.

Field studies

Two controlled, randomized, blinded field studies were performed in accordance with Good Clinical Practice.

In the Netherlands, 129 calves with maternally derived antibodies aged 4-11 days from three farms were randomly allocated to treatment (*n* = 64) and placebo (*n* = 65) groups. For 14 days after vaccination calves were monitored daily for general health, feed intake (score), rectal temperature (day 0 until day 4), respiratory disease score and lung auscultation. Blood samples were taken at Day 0 and Day 14 to determine antibody titres to BRSV and PI3. Maternally derived antibodies against BRSV and PI3 decreased slightly over the two weeks post vaccination, in both groups. No statistically significant differences were observed in feed intake score, rectal temperature and respiratory signs between the vaccinated and control calves. The results support the safety profile as observed in the laboratory studies. Adverse events observed in the field study are adequately captured in the SPC section 4.5.

In Portugal, a combined safety and efficacy study was performed. At the start of the experiment, 124 calves with maternally derived antibodies aged 5-11 days from three farms were included and randomly assigned to the vaccinate or control group. In total 21 calves were excluded from the study resulting in 58 calves in the vaccinated group and 45 in the control group. Calves in the vaccine group received one dose of vaccine in both nostrils without a nozzle at a titre of 5.5 $\log_{10}$ $TCID_{50}$ BRSV and 5.3 $\log_{10}$ $TCID_{50}$ PI3 per dose. The controls received reconstituted lyophilisate without vaccine viruses. Safety aspects were monitored for 14 days after vaccination, clinical examination was performed on days 0, 4 and 10, or daily if clinical signs were observed during the daily observation. Clinical examination included rectal temperature, breathing rate, coughing, nasal discharge and general impression resulting in a clinical score of 0-18. In both groups few clinical signs were recorded: coughing, enhanced breathing, nasal discharge, abnormal general impression, increased temperature. There was no significant difference in clinical score between vaccinates and controls.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

Laboratory Trials

Five development studies were performed for the BRSV component, to investigate the optimal route of administration, the dose, the influence of PI3 component on BRSV efficacy, administration with and without nozzle and administration in one nostril versus two nostrils. Based on the results of the development studies for BRSV it is recommended that the vaccine is administered directly intranasally into both nostrils of the calves (2 x 1ml), and that the vaccine should contain at least 4.7 – 4.8 $\log_{10}$ $TCID_{50}$ of the BRSV vaccine strain per dose. For the registered product, the intranasal administration into both nostrils is described in the SPC and package leaflet, and the registered minimum dose of the BRSV vaccine is 5.0 $\log_{10}$ $TCID_{50}$..

Two development studies were performed for the PI3 component in order to confirm the minimum vaccine dose and investigate the application method (with or without nozzle). Based on the results of the development studies for PI3 it is recommended that the vaccine is administered directly intranasally into the nostrils of the calves (2 x 1ml), and that the vaccine should contain at least 4.4 $\log_{10}$ $TCID_{50}$ per dose of the PI3 vaccine strain. For the registered product, the intranasal administration into both nostrils is described in the SPC and package leaflet, and the registered minimum dose of the PI3 vaccine is 4.8 $\log_{10}$ $TCID_{50}$.

The onset of immunity for BRSV was tested in 24 colostrum deprived BRSV free calves aged 5-9 days, in a randomised, partially blinded (laboratory samples) controlled study. The dissolved vaccine used in this study contained 4.8 $\log_{10}$ $TCID_{50}$ per dose of the BRSV vaccine strain. At day 5 post vaccination, calves were intranasally challenged with a virulent BRSV strain. Even though the challenge at 5 days post vaccination did not lead to severe disease or heavy shedding of virus in the unvaccinated control animals, a statistically significant reduction in BRSV shedding was observed in the vaccinated group as well as a notable reduction in clinical signs. No difference in viral load in the lungs and lung pathology could be evidenced, this may have been due to the low virus replication rate in the study. Based on the results of the study it can be concluded that the onset of immunity for the BRSV component of Bovilis INtranasal RSP Live is five days after vaccination as shown by a significant reduction in shedding and a notable difference in clinical signs between vaccinated and control group.

The onset of immunity for PI3 was tested in 24 colostrum deprived, BRSV and PI3 seronegative calves, in a randomised, controlled, blinded study. The animals were divided over three groups of eight animals: one group was challenged at 7 days post vaccination (OOI7) one group at 9 days post vaccination (OOI9) and one group remained as unvaccinated challenge controls. The first two groups were vaccinated intranasally with a vaccine containing 4.8 (OOI9) or 4.9 (OOI7) $\log_{10}$ $TCID_{50}$ PI3. Statistically significant reduction in shedding was observed both at 7 and at 9 days post vaccination. The clinical signs were lower in OOI7 and OOI9 groups compared to controls, albeit statistical significance was only achieved in group OOI9. For clinical signs however, statistical significance is not a requirement of Ph.Eur. 1176. It can therefore be concluded that the onset of immunity against PI3 is sufficiently supported at 7 days post vaccination, when vaccine is applied at a titre of 4.8-4.9 $\log_{10}$ $TCID_{50}$/dose in animals without maternally derived antibodies from 1 week of age.

Two studies were performed in order to support the claimed 12 weeks duration of immunity against BRSV. In the first study the challenge was rather mild, judged by the mild clinical signs, the absence of a clear temperature increase and the low titres of challenge virus in nasal discharge in the control group. The vaccine group had lower clinical scores and BRSV shedding than the control group but the numerical differences were too low to reach statistical significance, with the exception of the difference in virus shedding on days 6 and 7 post challenge, as well as the odds for shedding on any of the days. A second study was performed using a different challenge strain. Colostrum deprived calves aged 7-8 days were included in the study and allocated to two groups (vaccinates and controls) of 14 animals. On study day 84 (12 weeks after vaccination) all calves were challenged intranasally with BRSV strain Odijk. At 12 weeks post vaccination, the efficacy of the vaccine was clearly shown in calves without maternally derived antibodies vaccinated with a low titre vaccine by statistically significant reduction in viral shedding in nasal secretion, viral load in the lungs, respiratory clinical signs and lung lesions compared to calves from the unvaccinated control group.

One study was performed in support of the claimed duration of immunity of 12 weeks for PI3. The randomised, blinded, controlled study was performed in 20 colostrum deprived calves. Animals were allocated to two groups: the youngest calves (5-7 days of age) formed the group that received an intranasal vaccination with vaccine BRSV PI3 on Day 0, and the second group consisted of 10 calves aged 9-13 days that remained unvaccinated. Twelve weeks after vaccination all animals were challenged by aerosol with virulent PI3. At 12 weeks post vaccination, the efficacy of the vaccine was clearly shown in calves without maternally derived antibodies against PI3, vaccinated with a below-minimum titre vaccine by a statistically significant reduction in viral shedding in nasal secretion, fever and respiratory clinical signs.

Two studies for BRSV and one study for PI3 were performed in maternally derived antibodies

positive calves, as part of the developmental studies. In the first study 8 calves with maternally derived antibodies were vaccinated at 12-16 days of age, and challenged at three weeks post vaccination. Clinical signs were similar between vaccinates and controls, but in the vaccinates the excretion of BRSV was significantly reduced, the BRSV titre in bronchoalveolar lavage fluid was lower and the affected lung area was also lower. The second study was a dose finding study, using BRSV doses of 4.2, 4.7 and 5.2 $\log_{10}$ $TCID_{50}$ Virus excretion was reduced in a dose-dependent way, with significance compared to controls only in the highest dose group. Similarly, titres in the bronchoalveolar lavage fluid were lower in the highest dose group compared to controls. For PI3, a study was performed with 8 calves with maternally derived antibodies aged 9 days. Vaccination occurred intranasally with or without nozzle with a vaccine with a below minimum PI3 titre. After challenge at three weeks after vaccination rectal temperatures were significantly lower in the vaccinates, PI3 nasal shedding was reduced in both groups but significance was only reached in the group that was vaccinated without a nozzle, although the odds of shedding was significantly reduced in both vaccinated groups. An analysis was performed using data from the above studies to investigate the possible influence of maternally derived antibodies (BRSV and PI3 neutralising antibody titres at the time of vaccination) on shedding of BRSV and PI3 virus after challenge. The analysis of MDA levels versus virus shedding shows no correlation for either BRSV or PI3, which indicates that there is no negative effect of MDA on vaccine efficacy.

Field Trials

In Portugal, a combined safety and efficacy study was performed. Farms were pre-screened for presence of BRSV and/or PI3, in order to increase the chance to have BRSV and/or PI3 present on the farms during the field efficacy study. In total, 124 calves with maternally derived antibodies aged 5-11 days from three farms were included and randomly assigned to the vaccinate or control group. In total 21 calves were excluded from the study resulting in 58 calves in the vaccinated group and 45 in the control group. Calves in the vaccine group received one dose of vaccine in both nostrils without a nozzle at a titre of 5.5 $\log_{10}$ $TCID_{50}$ BRSV and 5.3 $\log_{10}$ $TCID_{50}$ PI3 per dose. The controls received reconstituted lyophilisate without vaccine viruses. The percentage of positive nasal swabs samples for BRSV (around 40%) and PI3 (around 12%) was very similar between vaccinated and control groups. In the vaccinated group less clinical signs were observed, a higher percentage of calves had a score of 0. A protective effect of the Bovilis INtranasal RSP live vaccine could not be shown in this study due to a very low BRSV or PI3 infection pressure (no outbreaks occurred during the study). However, a notable difference in general clinical signs (total clinical score) and clinical signs associated specifically to BRD between vaccinates and controls was observed. The vaccine was safe in 5 to 11 days old calves.

No further efficacy field studies are performed, considering the difficulties associated with this type of field study, the number of laboratory studies performed and the results achieved, as well as the type of vaccine (individual application).

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).

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.

None.