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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Protivity lyophilisate and solvent for suspension for injection for cattle

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0454/001/DC
Name, strength and pharmaceutical form	PROTIVITY lyophilisate and solvent for suspension for injection for cattle
Applicant	Zoetis Belgium Rue Laid Burniat 1, B-1348 Ottignies-Louvain-La-Neuve Belgium
Active substances	Each dose of 2 ml vaccine contains: *Mycoplasma bovis* strain N2805-1, live (attenuated): 0.22 x 10^7 to 15.50 x 10^7 Colony Forming Units.
ATC Vetcode	QI02AE05
Target species	Cattle
Indication for use	For active immunisation of calves from 1 week of age to reduce clinical signs and lung lesions caused by *Mycoplasma bovis* infection.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the original procedure	5th April 2023
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	Belgium, Bulgaria, Cyprus, France, Germany, Greece, Hungary, Ireland, Italy, Luxemburg, Netherlands, Poland, Portugal, Romania, Spain, United Kingdom (Northern Ireland)

I. SCIENTIFIC OVERVIEW

The vaccine contains a live attenuated *Mycoplasma bovis* which is indicated for the immunisation of cattle from one week of age and presented in freeze-dried form in a vial to be reconstituted with a vial of solvent (water for injections).
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 (Summary of Product Characteristics).
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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

Each dose of 2 ml reconstituted vaccine contains:

Active substance (lyophilisate):
Mycoplasma bovis strain N2805-1, live (attenuated): 0.22 x 10^7 to 15.50 x 10^7 Colony Forming Units.

The lyophilisate is filled in glass type I containers, closed with bromobutyl rubber stopper and sealed with an aluminium cap. The solvent is filled in glass type I containers. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains is justified.

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 practices in 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 comply with 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 according to the “Guideline on requirements for the production and control of immunological veterinary medicinal products” (EMA/CVMP/IWP/206555/2010-Rev2).

Seed lots have been produced as described in the relevant guideline.

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 in line with the relevant requirements; any deviation from these requirements is justified. The tests performed are as follows:

Lyophilisate
- Appearance
- Viable CFU count
- Identity test
- Sterility: according to Ph. Eur. 2.6.1
- Determination of residual humidity: according to Ph. Eur. 2.5.12

Solvent
Tested according to Ph. Eur. 0169
Sterility: according to Ph. Eur. 2.6.1

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

G. Stability

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 for the lyophilisate and 5 years for the solvent) when stored under the approved conditions.

The vaccine must be used immediately after reconstitution.

III. SAFETY ASSESSMENT

The studies were performed according to the recommendations of Directive 2001/82, Annex I, Title II as amended by 2009/09/EC and the relevant guidelines.
All laboratory studies were completed according to the principles of Good Laboratory Practice. The methods used in the studies have been validated.

Laboratory trials

The overdose and single repeat dose study conducted in one-week old seronegative calves, showed that a three times repeated dose administration or a 10x overdose administration of the vaccine strain at maximum titre did not raise any safety concerns.

Injection site reactions were observed after each dose administration. In the repeat dose vaccinated group, a swelling (more than 5 cm in diameter) could very commonly be seen at the injection site and spontaneously resolved within 3 days after vaccination.
The maximum size of a nodule seen in the repeat dose administration group was 0.8 cm3, which could last between 1 to 5 days. In the 10x overdose group, swellings with a diameter of more than 5 cm were observed at the injection site and spontaneously resolved in 4 days. The largest volume of a nodule was 3.02 cm3 and lasted until 16 days after administration.
No lameness was observed. Coughing was only observed at one time point in one animal in the repeat dose and control group. Other clinical signs were mild and were observed throughout the different treatment groups. These clinical signs are as such not considered to be linked to vaccine administration.

Laboratory safety studies have been conducted to meet the requirements for live vaccines. No shed or spread of the *M. bovis* vaccine strain N2805-1 MSB+1 was observed when administered subcutaneously to six- to seven-day-old calves. After simultaneous subcutaneous and intramuscular administration of a very high dose (about 7x the proposed maximum dose) at low passage (MSB+3) it was shown that dissemination of the vaccine strain to some organs can occur. Within this study, nasal shedding was observed for at least 9 days post-vaccination in one vaccinated animal. However, the vaccine strain did not spread to in-contact control animals.
The reversion to virulence study demonstrated that the intranasal inoculation of animals with the vaccine strain and subsequent passaging did not induce an increase in virulence.
Besides the stability of the phenotype, additional testing on genetic stability showed that the five single point mutations in the vaccine strain were maintained throughout the five passages.

Overall, the vaccine proved to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under “adverse events”.

Field studies

Two field studies were conducted in the United States of America with the administration of 2 mL dose of vaccine (of maximum titre) twice with a 3-week interval to young calves. The first study was conducted in 714 animals (1 to 43 days old) vaccinated in three different geographical regions in the US. In this field study, one calf was found lame due to *M. bovis* and subsequently the vaccine strain was isolated from the affected joint. This was the only adverse event that could be associated with the vaccine administration. In the second field study, 97 animals (4 to 7 days old) were vaccinated and observed for a four-month period. No adverse events of an unexpected type or frequency were detected during the observation period. All adverse events noted in the vaccinated animals resolved and were unrelated to the vaccine strain. No lameness was observed throughout the study

period. *Mycoplasma bovis* was never recovered in any of the deep nasal swabs taken, confirming that the *M. bovis* vaccine strain does not shed from vaccinated animals when administered at a commercial dose.

Two field studies were conducted in the European Union with the administration of 2 mL dose of vaccine twice with a 3-week interval to young calves. One study was conducted in 102 animals (5 to 14 days old) in the United Kingdom using a commercial vaccine with an intermediate titre (1.32×10^7 CFU/dose).
The second study was performed in 122 animals (2 to 5 weeks old) in the Netherlands using a commercial vaccine with an intermediate titre (1.52×10^7 CFU/dose).

The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet as follows:

3.6 Adverse events

Cattle:

Very common (>1 animal / 10 animals treated):	*injection site swelling*[1]
Common (1 to 10 animals / 100 animals treated):	*injection site pain*[2] *injection site warmth*[2] *injection site nodule*[3]
Uncommon (1 to 10 animals / 1,000 animals treated):	*lameness*

[1]More than 5 cm in diameter observed on the day of vaccine administration and resolving spontaneously within 3 days.
[2]On the day of vaccine administration.
[3]Less than 0.8 cm^3 in volume observed from 10 days after vaccination and lasting between 1 to 5 days.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder <or its local representative> or the national competent authority via the national reporting system. See also section "Contact details" of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

3.8 Interaction with other medicinal products and other forms of interaction

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No other adverse events than those mentioned in section 3.6 "Adverse events" were observed after administration of a 10-fold overdose of the vaccine. Swelling at the injection site may have a diameter of more than 5 cm and will spontaneously resolve in 4 days. The volume of the observed nodule may be up to 3 cm^3, can be observed from 5 days post vaccination and may last until 16 days after administration of a 10-fold overdose of the vaccine.

Ecotoxicity

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

Warnings and precautions as listed in the product literature for its disposal are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

In laboratory conditions, efficacy was demonstrated in a challenge study in which 40 vaccinates and 40 control animals (seronegative calves 7 to 12 days old) were challenged with a challenge strain of US origin. From the results of the study, it can be concluded that after completion of the basic vaccination scheme a reduction in clinical signs and lung lesions caused by *M. bovis* infection is demonstrated. A significant reduction of the hyperthermia, and of the duration of clinical signs (attitude and respiratory effort) and of number of animals with lung lesions was observed when the challenge is done 12 days after the basic vaccination scheme.
During early development, a preliminary efficacy study in which the calves received only one dose of vaccine subcutaneously did not show significant differences between vaccinates and controls.
The applicant also provided a study involving 64 vaccinates and 37 control animals (seronegative calves 7 to 12 days old). The vaccinates received one dose of

vaccine by intranasal route of administration and the calves were challenged with a field strain isolated in Italy in 2000. A significant reduction of hyperthermia, duration of clinical signs and of number of animals with lung lesions was observed. However, the data are considered as supportive only, as the field strain was not able to induce clinically relevant levels of lung lesions.

Studies to establish the duration of immunity and the efficacy in presence of maternally-derived antibodies have not been performed, which is considered acceptable based upon the approved MUMS classification of the vaccine (and the associated data reductions) and the clear description in the SPC/PI on the available data in this regard.

Field Trials

Two field studies were conducted in the European Union in commercial farms with history of *M. bovis* outbreaks but in both studies, exposure to *M. bovis* happened before completion of the full two dose vaccination course.
In addition, no clear clinical exposure to *M. bovis* was observed in the study taking place at a UK dairy farm. The study conducted in a Dutch veal feedlot was confounded by the presence of multiple concurrent pathogens. Therefore, no conclusions could be made on efficacy in both studies.

The following conclusions can be drawn from the results of the studies concerning onset of immunity, indications for use and immunisation scheme:

3.2 Indications for use for each target species

For active immunisation of calves from 1 week of age to reduce clinical signs and lung lesions caused by Mycoplasma bovis infection.

Onset of immunity: 12 days after the basic vaccination scheme.
Duration of immunity: has not been established.

3.9 Administration routes and dosage

Vaccinate cattle by the subcutaneous route in the neck.

Reconstitute the lyophilisate with the solvent to obtain a suspension for injection.

After reconstitution, the suspension should be pinkish to orange-brown turbid in color.

Basic vaccination scheme:

Two doses, each of 2 ml, should be administered 3 weeks apart to calves from 1 week of age. The second dose should preferably be administered on the alternate side of the neck.

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 benefit risk 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 (http://www.hma.eu/vmriproductindex.html).

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.