ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Rispoval RS + PI3 Intranasal

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0224/001/MR
Name, strength and pharmaceutical form	Rispoval RS + PI3 Intranasal Powder and diluent for suspension for intranasal application.
Applicant	Pfizer Ltd Ramsgate Road Sandwich Kent CT13 9NJ
Active substances	Modified live Bovine Parainfluenza type 3 (PI3), thermosensitive strain RLB103 Modified live Bovine Respiratory Syncytial (BRS) Virus strain 375
ATC Vetcode	QI02AD07
Target species	Cattle
Indication for use	For active immunisation of maternally derived antibody positive or negative calves from 3 weeks of age against BRSV and PI3.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (HMA(v)) website (**WWW.HEVRA.ORG**).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application for marketing application in accordance with Article 32 (2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	05th October 2006
Date product first authorised in the Reference Member State (MRP only)	11th October 2005
Concerned Member States for original procedure	Austria Belgium Czech Republic Estonia France Germany Greece Hungary Ireland Italy Latvia Lithuania Luxembourg Netherlands Poland Portugal Slovakia Slovenia Spain

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 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 contains modified live Bovine Parainfluenza type 3 (PI3) virus, thermosensitive strain RLB103, between $10^{5.0}$ and $10^{8.6}$ $CCID_{50}$ and modified live Bovine Respiratory Syncytial (BRS) virus strain 375, between $10^{5.0}$ and $10^{7.2}$ $CCID_{50}$, as well as diluent containing sodium chloride and water for injections.

The container/closure system consists of the freeze dried component presented in 15ml (5 doses) and 23ml (5 doses) vials of Type 1 glass. The stoppers are made from Bromobutyl rubber covered with an aluminium varnished cap with a central hole. The liquid fraction is presented in 15ml (5 doses) vials of Type 1 glass. The stoppers are made from Chlorobutyl rubber and covered with an aluminium varnished cap with a central hole. A nasal applicator is provided in separate packaging. The particulars of the containers and controls performed are provided and conform to the regulation.

The choices of vaccine strains are 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 practice from 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

The active substances are BRSV and PI3 which are established active substances. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with the European Pharmacopeia monographs 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 Ph. Eur; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System 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 conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular sterility, extraneous agent testing, Mycoplasma testing, viral content and identity.
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 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 when stored under the approved conditions.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

III. SAFETY ASSESSMENT

Details of the batches of Rispoval RS + PI3 Intranasal used in the laboratory safety studies were provided.

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 one study. Safety was assessed clinically, over an appropriate time course, through observation and physical examination. The

investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. There were no adverse effects seen following administration of one dose, an overdose and a repeated dose in healthy animals of the minimum age for which the vaccine is recommended.

The company did not evaluate the incidence of hypersensitivity reactions. However, no abnormal reactions were observed in vaccinated animals.

The SPC reflects the lack of hypersensitivity data as follows:

Published evidence shows that on rare occasions repeated exposure to RSV may trigger hypersensitivity reactions.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals.

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.

For both live strains included in the vaccine:
Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strains. In regards to the studies undertaken for the spread of the vaccine, the first part of the study showed that the non-vaccinated animals that had been in contact with the vaccinated animals shed[1] the virus on at least one day, demonstrating that the virus had spread.

The SPC reflects these findings as shown below.

Viruses can spread from vaccinated to non-vaccinated calves and may cause a serological response, but without causing clinical signs. In laboratory experiments, shedding was observed for BRSV and PI3 viruses up to 11 and 7 days respectively after vaccination with one dose containing the maximum virus content. Animals should preferably be vaccinated at least 10 days before a period of stress or high infection risk like re-grouping or transport of animals, or at the start of the autumn season. To achieve optimal results, it is recommended to vaccinate all calves within the same herd.

The second part of the study showed that both viruses are excreted via the nasopharyngeal route, but offers no further information on dissemination within the tissues of the animal after intranasal vaccination. The company provided information from another study using a similar licensed product called Rispoval 4 in which the vaccine was administered intramuscularly, and no dissemination was seen. The company state that since this was the most invasive route and no dissemination was found, then it is unlikely that there will be dissemination via the intranasal route. This justification was accepted.

[1] When an animal 'sheds' virus it excretes it e.g. in urine or faeces, into the environment.

In the reversion to virulence studies the results showed that there were no signs of reversion to virulence.

The substances of Rispoval RS+PI3 Intranasal used are not listed in the MRL regulations. 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

Field trials were conducted on the vaccine under commercial conditions to assess the safety and efficacy of Rispoval RS+PI3 for cattle under field conditions.

Safety was assessed on the basis of clinical observations until the end of the study for systemic and local reactions.

No temperature rises or clinical signs were seen in the vaccinates, and the company concluded that a single dose administered intranasally has shown to be safe in minimum age animals under field conditions.

The company also did not evaluate the incidence of hypersensitivity reactions. However, no abnormal reactions were observed in the vaccinated animals.

The SPC reflects the lack of hypersensitivity data as follows:

Published evidence shows that on rare occasions repeated exposure to RSV may trigger hypersensitivity reactions.

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 assessment concluded that the risk to the environment from the use of Rispoval RS+PI3 Intranasal in cattle is minimal. Normal methods for the disposal of any unused product are recommended in the SPC.

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)

Laboratory Trials

The applicant has conducted dose determination and confirmation studies which show that the efficacy of the product has been demonstrated in four laboratory studies in accordance with the relevant requirements.
The first study was to determine the onset of immunity of the PI3 component. The animals used were conventional, colostrum derived calves confirmed to be seronegative or with low antibody titres to PI3 before the start of the study. The animals were challenged intranasally (both nostrils) with either 2ml of vaccine or saline. The animals were observed for depression, respiration, cough and nasal discharge, and the signs were categorised as either present or absent. Rectal temperatures were also monitored. The results presented indicated a reduction of excretion in vaccinated calves and supports the claim of a reduction in virus shedding and duration of shedding by 10 days post vaccination.

The second study was to determine the onset of immunity of the BRSV component. The animals used were colostrum derived calves, and confirmed to be seronegative or with low antibody titres to BRSV before the start of the study. The animals were challenged intranasally (both nostrils) with either 2ml of vaccine or saline. The animals were observed for depression, respiration, cough and nasal discharge, and the signs were categorised as absent, mild, moderate, or severe. Rectal temperatures were also monitored. The results presented indicate a reduction of excretion in vaccinated calves and supports the claim of reduction in virus shedding and duration of shedding 10 days after vaccination.

The third study was to determine the duration of immunity for PI3. The animals used were confirmed to have MDA against PI3 before the start of the study. The animals were challenged intranasally (both nostrils) with either 2ml of vaccine or saline. The animals were observed for depression, respiration, cough and nasal discharge, and the signs were categorised as either present or absent. Rectal temperatures were also monitored. These data support the claim for a reduction in nasal shedding of PI3 when vaccination is carried out in the presence of MDA.

The fourth Study was to determine the duration of immunity for BRSV. The animals used were confirmed to have MDA against BRSV before the start of the study. Calves were vaccinated at the end of October which is the start of the “respiratory disease season” and is the point at which most calves would be vaccinated in the field. Calves were also vaccinated at 3 weeks of age, when levels of MDA to BVDV are still high, thus the vaccine is being tested under conditions where the maximum interference from MDA could occur. The animals were challenged intranasally (both nostrils) with either 2ml of vaccine or saline. The animals were observed for depression, respiration, cough and nasal discharge, and the signs were categorised as either present or absent. Rectal temperatures were also monitored. These data support the claim for a reduction in nasal shedding of BRSV when vaccination is carried out in the presence of MDA.

Field Trials

The company has conducted two field studies.

The first trial was to determine the field efficacy and safety of a modified live PI3 and BRSV vaccine administered as a single intranasal dose to calves at minimum age. It is stated that the site has a long history of respiratory disease in calves during the winter housing period. The animals were 13 to 27 days old and were of various breeds. Seventy-three animals were dosed with either 2ml of vaccine or saline intranasally. General health was observed for signs of respiratory disease.

The second trial was to determine the field efficacy of a modified live PI3 and BRSV vaccine administered as a single intranasal dose to calves at minimum age. The site has a long history of respiratory disease in autumn born, winter house calves. Ninety-two animals were included in the trial at ages of 14 to 27 days. They were dosed with 2ml of either saline or vaccine intranasally. Vaccinates and controls were kept in separate fields and general health was observed once daily.

From an efficacy point of view the trials was inconclusive as there were no statistically significant differences between vaccinated and control animals. There was also no BRSV or PI3 challenge observed during the trials. Despite this it was concluded during the national procedure that the laboratory trials supported the following claim on the SPC.

For active immunisation of maternally derived antibody positive or negative calves from 3 weeks of age against BRSV and PI3, to reduce mean titre and duration of excretion of both viruses. Onset of immunity is within 10 days following vaccination. A statistical reduction in the amount of BRSV shed was also observed within 5 days after vaccination in seronegative animals. The duration of immunity is at least 9 weeks following a single dose.

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 Medicines 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.

None