

**IPAR**



## **Publicly Available Assessment Report for a Veterinary Medicinal Product**

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**Bovilis Bovipast RSP suspension for injection**

**PRODUCT SUMMARY**

Name, strength and pharmaceutical form	<p>Bovilis Bovipast RSP</p> <p>Inactivated Bovine Respiratory Syncytial Virus, strain EV908: <math>10^{5.5}</math> TCID<sub>50</sub>* - <math>10^{6.4}</math> TCID<sub>50</sub></p> <p>Inactivated Parainfluenza-3-Virus, strain SF-4 Reisinger: <math>10^{7.3}</math> TCID<sub>50</sub>- <math>10^{8.3}</math>TCID<sub>50</sub></p> <p>Inactivated. <i>Mannheimia (Pasteurella) haemolytica</i> A1, strain M4/1: <math>9 \times 10^9</math> cells</p> <p>*Tissue culture infective dose 50%</p> <p>Suspension for injection</p>
Active substance(s)	<p>Inactivated Bovine Respiratory Syncytial Virus, strain EV908</p> <p>Inactivated Parainfluenza-3-Virus, strain SF-4 Reisinger</p> <p>Inactivated. <i>Mannheimia(Pasteurella) haemolytica</i>A1, strain M4/1</p>
Applicant	<p>Intervet Ireland Ltd.</p> <p>Magna Drive</p> <p>Magna Business Park</p> <p>Citywest Road</p> <p>Dublin 24</p>
Date of Authorisation	6th June 2000
Target species	Cattle
Indication for use	<p>For the active immunisation of cattle against:</p> <ul style="list-style-type: none"> <li>-Parainfluenza 3 virus, to reduce infection,</li> <li>-Bovine Respiratory Syncytial virus, to reduce infection and clinical signs,</li> <li>-<i>Mannheimia haemolytica</i> serotype A1, to reduce infection, mortality, clinical signs, lung lesions and bacterial invasion of the lung caused by serotypes A1 and A6.</li> </ul> <p>Cross-reactive immunity to the A6 serotype of <i>M.haemolytica</i> has been demonstrated in a challenge experiment under laboratory conditions after primary course of vaccination.</p> <p>Approximately two weeks after completion of the basic immunisation programme, the humoral immune response against BRS-Virus and PI-3-Virus is at its highest level. The duration of protective</p>

	immunity has not been established in challenge experiments.
ATCvet code	QI02AL04
Date of completion of the original mutual recognition procedure	25 May 2000 (UK) 06 June 2000 (IE)
Date product first authorised in the Reference Member State (MRP only)	25 June 1999
Concerned Member States for Repeat Use procedure	Belgium, Denmark, Finland, Greece, Ireland (now RMS), Italy, Luxembourg, Norway, Poland, Spain, Sweden UK added via RMS change

## PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

## I. SCIENTIFIC OVERVIEW

The product is an adjuvanted vaccine containing Bovine Respiratory Syncytial (BRS) Virus strain EV908, inactivated Parainfluenza-3 (PI-3) Virus strain SF-Reisinger and inactivated *Mannheimia (Pasteurella) haemolytica* serotype A1, strain M4/1. The product is indicated for the active immunisation of cattle against; PI-3-virus to reduce infection; BRS virus to reduce infection and clinical signs; and *M. haemolytica* serotype A1, to reduce infection, mortality, clinical signs, lung lesions and bacterial invasion of the lung caused by serotypes A1 and A6.

Cross-reactive immunity to the A6 serotype of *M. haemolytica* has been demonstrated in a challenge experiment under laboratory conditions after a primary

course of vaccination. Approximately two weeks after completion of the basic immunisation programme, the humoral immune response against BRS-Virus and PI-3-Virus is at its highest level. The product is given as an immunising dose of 5 ml, via subcutaneous injection into the side of the neck. Animals from approximately 2 weeks of age should receive 2 vaccinations, separated by an interval of approximately 4 weeks. A booster dose may be given approximately 2 weeks before each risk period, (e.g. transport, change of housing, introduction to a herd).

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 benefit/risk analysis is in favour of granting a marketing authorisation.

## II. QUALITY ASPECTS

### A. Composition

The product contains per dose (5 ml) inactivated BRS virus, strain EV908 at least  $10^{5.5}$  TCID<sub>50</sub>[1], max  $10^{6.4}$  TCID<sub>50</sub>, inactivated PI3 virus, strain SF-4 Reisinger at least  $10^{7.3}$  TCID<sub>50</sub> max  $10^{8.3}$  TCID<sub>50</sub>, inactivated *M. haemolytica* A1, strain M4/1  $9 \times 10^9$  cells. The adjuvantia are aluminium hydroxide 37.5 mg and quil A (Saponin) 0.625 mg. Thiomersal is included as a preservative. The container/closure system is a 50 ml bottle of Type I glass, closed with injection stoppers of Type I rubber, sealed with an aluminium cap.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the adjuvantia, vaccine strains, inactivating agent and the presence of preservative 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. 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 established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the

principles of good manufacturing practice. Starting materials of non-biological origin used in production comply with European guidelines.

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 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.

***H. Genetically Modified Organisms***

Not applicable.

***J. Other Information***

Unopened, the vaccine has a shelf-life of 28 months. The contents of the bottle should be used within 10 hours of first broaching the cap. Store at +2°C to +8°C, protect from sunlight and freezing.

[1] TCID<sub>50</sub> – Tissue culture infective dose 50%.

### **III. SAFETY ASSESSMENT**

**Laboratory trials**

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal were demonstrated in young cattle. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. No adverse reactions attributable to the vaccine were seen, any slight reactions with regard to a slight, transient rise in body temperature, or local reactions at the injection site are cited on the SPC.

Effects on reproductive performance were examined, the product is safe for use during pregnancy or lactation.

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 large series of field studies were presented for the product, with the batch vaccine used at maximum potency. No adverse reactions attributable to the vaccine were seen.

**Ecotoxicity**

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was 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****Studies****Laboratory Trials**

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

Four vaccine batches, BPP06 which contained minimum levels of viral components and BPP01, IRP-1 and IRP-10, which contained moderate levels of viral components were used in efficacy studies. All vaccine batches contained the fixed amount of *M.haemolytica* cells. Vaccine batches BPP01, IRP-1 and IRP-10 were used only to determine the efficacy of the *M.haemolytica* component. In addition, three batches of a monovalent *M.haemolytica* vaccine were used to determine the efficacy of the *M.haemolytica* component.

The efficacy was evaluated in challenge experiments.

In one study, a suitable number of young cattle with low titres of maternally derived antibody (MDA) were vaccinated twice with 5 ml doses of Bovilis Bovigrip,

(equivalent to the marketed product). An unvaccinated control group was also included. All animals were challenged with BRS virus 3 weeks after vaccination, and challenged again 3 weeks after this with PI3 virus. The animals were monitored for antibody titers, clinical signs and virus shedding. After vaccination the antibody titres against BRSV and PI3 were shown to be higher in the vaccinated animals than in the unvaccinated control animals. After challenge infection, the efficacy of the vaccine was demonstrated by reduction of clinical signs and reduction of shedding of BRSV and PI3 virus.

In a second study, young animals were vaccinated twice with Bovipast RSP within a four week interval. Some animals were kept as unvaccinated controls. A proportion of animals had high MDA at the commencement of the trial, some had low MDA. All animals were challenged with BRSV three weeks after vaccination, and three weeks after that, challenged with PI3 virus. The animals were monitored for antibody titers, clinical signs and virus shedding.

Post-vaccination, the vaccinated animals had higher antibody titres for BRSV compared to unvaccinated controls. Animals with low levels of MDA at the time of vaccination developed a higher humoral response to the vaccine compared to those with high levels of MDA. Antibody titers for PI3 virus were comparable after vaccination, but significantly higher in the vaccinated animals compared to the controls after challenge.

After challenge infection, the efficacy of the vaccine was shown in MDA positive animals by reduction of clinical signs and reduction of shedding of BRS virus and PI3 virus.

Similarly designed studies demonstrated that the vaccine gave considerable protection against homologous and heterologous *M.haemolytica* challenge. The challenges were performed between two and 6 weeks after full vaccination using *M.haemolytica* serotypes A1 and A6 isolates as challenge strains. Vaccination led to a reduction of infection, mortality, clinical signs, lung lesions and bacterial invasion of the lung caused by serotypes A1 and A6.

### **Field Trials**

One field trial was conducted evaluating the onset and duration of immunity of the vaccine in young animals vaccinated according to the recommended vaccination schedule, two-times approximately 4 weeks apart. Another field trial evaluated the onset of immunity of the vaccine in young animals in the presence of maternally derived antibodies. The animals in the latter trial were vaccinated three-times, all approximately 4 weeks apart. In both trials, some animals were kept as unvaccinated controls. Blood samples were taken at appropriate time points, before and after vaccinations.

Qualitative and quantitative serological test results demonstrate that the vaccine is effective in inducing an appropriate immune response to BRSV, PI3 virus and *M.haemolytica* in the presence of MDA, when used as recommended.

## 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.

## VI. 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 HPRA website.

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.

### ***Safety/Efficacy Changes***

<b>Summary of change</b>	<b>Approval date</b>
<p>To add the claim that Bovilis Bovipast RSP is compatible for use with Bovilis IBR Marker Live.</p> <p>HPRA case reference number 7001665</p>	<p>19<sup>th</sup>April 2007</p>