IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Pneumovac

PRODUCT SUMMARY

EU Procedure number	IE/V/0638/001/DC
Name, strength and pharmaceutical form	Pneumovac
Active substances(s)	Bovine Respiratory Syncytial Virus, Strain Bio-24, inactivated, Bovine parainfluenza 3 virus, strain bio-23, inactivated, *Mannheimia haemolytica*, serotype A1 strain dsm 5283, inactivated
Applicant	Animal Health Distributors Limited Tullow Industrial Estate Bunclody Road Tullow Carlow R93WOD8 Ireland
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Date of completion of procedure	01/07/2020
Target species	Cattle
Indication for use	For active immunisation of cattle against: Bovine parainfluenza 3 virus, to reduce the quantity and duration of virus excretion. Bovine respiratory syncytial virus, to reduce the quantity and duration of virus excretion. *Mannheimia haemolytica* Serotype 1A, to reduce clinical signs and lung lesions. *Onset of immunity:* 3 weeks after primary vaccination course *Duration of immunity:* 6 months after primary vaccination course
ATCvet code	QI02AL04
Concerned Member States	UK

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 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. Qualitative and Quantitative Particulars
The product contains the following active substances per 2 ml vaccine dose:
Bovine respiratory syncytial virus inactivated, strain BIO 24 RP ≥ 1*
Bovine parainfluenza 3 virus inactivated, strain BIO 23 RP ≥ 1*
Mannheimia haemolytica inactivated, Strain DSM 5283, serovar 1A RP ≥ 1*
*RP - Relative Potency (ELISA) 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.

Aluminium hydroxide (8 mg per 2ml dose) and Quillaja saponin (Quil A) (0.4 mg per 2ml dose) are used as adjuvants.
Thiomersal is included in the vaccine as a preservative. Formaldehyde used during production of the active substance *Mannheimia haemolytica* can be present in the vaccine (up to 1 mg per 2 ml dose)

The container/closure system consists of 10 ml hydrolytic Type I glass vials containing 5 doses and 50 ml and 100 ml hydrolytic Type II glass vials for the 25 and 50 doses of vaccine presentations, respectively.
The vaccine can also be packaged in the following HDPE plastic containers: 15ml vials containing 10 ml (5 doses), 60ml vials containing 50ml (25 doses) and 120ml vials containing 100ml (50 doses).
All containers are closed with chlorobutyl rubber stoppers and secured with aluminium seals.

The choice of the vaccine strains, adjuvant, inactivating agent and formulation are justified. The presence of preservative are also justified.
The inactivation process and the detection limit of the control of inactivation are acceptably 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 in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data for the manufacturing process has 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 Ph. Eur. monographs or in-house specifications.
Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.
Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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 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. The tests include general characteristics of the finished product e.g. appearance, usable volume test, pH, container air-tightness, identification of active substances including identity testing and potency testing, sterility and endotoxin testing in line with the relevant Ph. Eur. monograph, including identification and assay of adjuvants and preservatives.
The demonstration of the batch to batch consistency is based on the results of 3 consecutive batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F. Stability
The active substances are fully tested to ensure compliance with specifications prior to their use in manufacture of the product.

Stability data on the finished product has 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 vaccine is supported by the data provided.

G. Other Information
Not applicable.

III. SAFETY ASSESSMENT

Safety data for Pneumovac suspension for injection for cattle has been evaluated in studies using a larger, 4 component inactivated vaccine, Pneumovac Plus suspension for injection for cattle (VPA 22715/002/001). Pneumovac is a 3 component inactivated vaccine which contains bovine parainfluenza 3 (PI-3) virus, bovine respiratory syncytial virus (BRSV), and *Mannheimia (Pasteurella) haemolytica* Serotype 1A, but which lacks the bovine viral diarrhoea (BVD) virus component that is included in Pneumovac Plus. As the larger multi-component vaccine, Pneumovac Plus, represents a worst-case scenario for safety evaluation of the 3 component 'fall-out' vaccine, Pneumovac, the data is considered relevant for the fall-out product. Therefore, it is considered acceptable to extrapolate the safety profile of Pneumovac Plus to that of Pneumovac, in accordance with the principles outlined in EMA/CVMP/IWP/594618/2010 'Requirements for combined vaccines and associations of IVMPs'.
Pneumovac is intended for use in cattle from 2 weeks of age and is administered subcutaneously as an initial 2 ml vaccination followed 3 weeks later with a second 2 ml vaccination. Revaccination with a single dose is recommended within a period of 6 months after completion of the primary vaccination.
This inactivated vaccine contains 3 antigens plus aluminium hydroxide and quillaja saponin (Quil A) as adjuvants and thiomersal and formaldehyde as excipients.
The laboratory and field safety studies were conducted in accordance with GLP and GCP, respectively.

Laboratory Trials

Three laboratory studies were conducted, in which the safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal was demonstrated in calves from 2 weeks of age. In these studies, a vaccine batch representative of maximum potency for all antigens included in the vaccine was administered to animals. The calves included were seronegative, or had low levels of antibodies, for the antigens included in the vaccine. Safety monitoring included daily observations for 14 days for the assessment of general health and local reactions, and monitoring of rectal temperature at appropriate time points.
The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
Overall, the vaccine was shown to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC and package leaflet.

In the absence of sufficient data to investigate the safety of use during pregnancy and lactation in accordance with requirements, the SPC carries a statement 'Do not use during pregnancy and lactation.'

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

No studies on residues have been performed. All components of the vaccine are either allowed substances according to Table 1 of Regulation (EC) No. 37/2010, or are substances considered as not falling within the scope of Regulation (EC) No. 470/2009. The proposed withdrawal period 'zero days' is accepted.

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

Field Studies

The safety of vaccination was evaluated under field conditions in two field trials conducted in one EU Member State. The vaccine was administered according to the recommended schedule of 2 doses, separated by an interval of 3 weeks, and administered by the subcutaneous route to calves from 2 weeks of age or pregnant cattle. All animals were observed for adverse reactions during the study and reproductive parameters were evaluated in pregnant animals. Overall, under field conditions the vaccine was shown to be well tolerated in the target species. However, in the absence of sufficient data to investigate the safety of use during pregnancy and lactation in accordance with requirements, the safety of use in this category of target species has not been adequately demonstrated and therefore use is not recommended during pregnancy or lactation.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that while the main risk to the user is accidental self-injection, the components of the vaccine are not expected to present a risk to the user. It is accepted that the use of Pneumovac does not pose a risk to the user, when used in accordance with recommendations.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

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. Pneumovac is an inactivated vaccine (which does not contain any live viral / bacterial antigens), therefore excretion or shedding of vaccine strains into the environment is not possible. The assessment concluded that Pneumovac has no undesirable effects on the environment. It is accepted that the vaccine is not expected to present a risk to the environment when used in accordance with recommendations.
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

IV.B Clinical Studies

Laboratory Trials

Pneumovac is intended for use in cattle from 2 weeks of age and is administered subcutaneously as an initial 2 ml vaccination followed 3 weeks later with a second 2 ml vaccination. The vaccine is intended for the active immunisation of cattle against the following: bovine parainfluenza 3 (PI-3) virus, bovine respiratory syncytial virus (BRSV) and *Mannheimia (Pasteurella) haemolytica* Serotype 1A. The onset of immunity is 3 weeks after basic immunisation and the duration of immunity is 6 months after basic immunisation. Revaccination is recommended and consists of a single vaccination within a period of 6 months after completion of the primary vaccination.
Similar to that discussed in Part III Safety, the efficacy of Pneumovac suspension for injection for cattle has been evaluated in studies using a larger, 4 component inactivated vaccine, Pneumovac Plus suspension for injection for cattle. Pneumovac is a 3 component inactivated vaccine which contains bovine parainfluenza 3 (PI-3) virus, bovine respiratory syncytial virus (BRSV), and *Mannheimia (Pasteurella) haemolytica* Serotype 1A, but which lacks the bovine viral diarrhoea (BVD) virus component that is included in Pneumovac Plus. It was justified that the presence of the BVDV component (in Pneumovac Plus) was not expected to affect the immune response to any of the other vaccine components, and therefore it was accepted that the efficacy data generated using Pneumovac Plus could be extrapolated to Pneumovac, in accordance with the principles outlined in EMA/CVMP/IWP/594618/2010 'Requirements for combined vaccines and associations of IVMPs'.
The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements, including the specific European Pharmacopoeia (Ph. Eur.) monographs for *M. haemolytica* (1944).
Efficacy was tested in the laboratory following administration of vaccine by the subcutaneous route to calves from 2 weeks of age. The vaccine batches used in the laboratory efficacy studies were at minimum potency for all antigens.

Onset of immunity:
The efficacy in the target species was demonstrated by means of challenge trials. The design of each study was similar for each of the studies for the viral antigenic components; 10 seronegative calves were included in each study; 5 calves were vaccinated in accordance with recommendations (two dose basic vaccination scheme) and five calves were included as negative controls. Three weeks after the second dose, in each study all animals were challenged with a virulent strain of the virus that the study was intended to demonstrate protection against (i.e., PI-3 virus or BRSV*)*. General health, clinical signs, rectal temperature, serology, and virus isolation from nasal swabs were evaluated following challenge. The differences in these parameters were compared between the vaccinated and control groups using appropriate statistical analyses.
It was concluded that the data supported a claim for a reduction in the quantity and duration of virus excretion due to bovine PI-3 virus infection and a reduction in the quantity and duration of virus excretion due to BRSV infection.
The efficacy in the target species against the *Mannheimia haemolytica* component was demonstrated by challenge test in accordance with the method stated in the Ph. Eur. Monograph 1944. Sixteen seronegative calves were included; 8 calves were vaccinated according to the recommended schedule and 8 calves were maintained as negative controls. Three weeks after the second dose, all animals were challenged with a virulent strain of *Mannheimia haemolytica*. General health, clinical signs of respiratory disease, rectal temperature, serology were evaluated, in addition to lung lesion scores at day 7 post-challenge. The

differences in these parameters were compared between the vaccinated and control groups using appropriate statistical analyses. There was a significant reduction in lung lesion scores and a significant reduction in clinical signs in vaccinated calves compared to controls following *M. haemolytica* challenge, thus supporting the claim for a reduction in clinical signs and lung lesions for this antigenic component.
Laboratory studies have not been provided to evaluate the influence of maternally derived antibodies on the efficacy of the vaccine in the target species and therefore appropriate warnings are included in the relevant section of the SPC.

Duration of immunity
The duration of immunity of 6 months after primary vaccination was demonstrated for each antigenic component using similar study designs as for the onset of immunity studies, with challenge instead performed at 6 months following completion of the two dose basic vaccination scheme.
The efficacy of a single booster injection at six months after the completion of the basic vaccination scheme in support of the proposed revaccination schedule was evaluated by the serological response only (no challenge data). This information is clearly indicated in the SPC section 4.9.

Field Trials

The applicant has conducted a combined field safety and efficacy trial in one EU Member State, whereby the vaccine was administered according to the recommended schedule of 2 doses, 3 weeks apart, and administered by the subcutaneous route to calves from 2 weeks of age or pregnant cattle. Efficacy was assessed based on serology and monitoring of clinical signs however correlation of specific antibody responses produced by vaccination with Pneumovac to protection against PI-3, BRSV and *M. haemolytica* was not provided. In the absence of any such correlation, in addition to an absence of natural challenge on the farms included, the field efficacy study is considered supportive only.

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.

Changes:
None.