Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Poulvac Bursa Plus Lyophilisate for Suspension in Drinking Water

PuAR correct as of 23/01/2018 when RMS was transferred to DE. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0335/001/MR
Name, strength and pharmaceutical form	Poulvac Bursa (DK) Poulvac Bursa Plus vakcina A.U.V. (HU) Poulvac Bursa Plus (all other countries) Lyophilisate for suspension in drinking water. Live Infectious Bursal Disease virus, strain V877. Lyophilisate for suspension for oral administration in drinking water.
Applicant	Fort Dodge Animal Health Flanders Road Hedge End Southampton Hampshire SO30 4QH
Active substance(s)	Live Infectious Bursal Disease virus, strain V877
ATC Vetcode	QI01AD09
Target species	Chickens
Indication for use	For the active immunisation of chickens with maternal antibody levels of ≤ 500 ELISA units, to reduce mortality and bursal lesions of Gumboro disease. The onset of immunity has been shown by challenge from fourteen days after vaccination and the duration of immunity is thirty-two days.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 32(2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	4th March 2010.
Date product first authorised in the Reference Member State (MRP only)	3rd February 1998.
Concerned Member States for original procedure	Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

Poulvac Bursa Plus is intended for use in healthy, susceptible broiler chickens from ten days of age. The vaccine confers active immunisation against mortality and clinical symptoms caused by infectious bursal disease (Gumboro disease). Onset of immunity is fourteen days after inoculation, and duration of immunity is at least thirty-two days. The vaccine is administered via drinking water as a single dose and used at a dose rate of $10^{2.2}$-$10^{3.4}$ EID_{50}.[1]

Poulvac Bursa Plus is designed to bestow maximum protection against infectious bursal disease virus (IBDV), specifically with respect to any maternally derived antibodies (MDA), which may be present. Serotype 1 IBDVs are the only IBDV infectious to chickens, and are subtyped as classic, antigenic-variant and very virulent. These very virulent viruses are difficult to manage in Europe and present a significant economic threat. Poulvac Bursa Plus Lyophilisate for suspension in drinking water was manufactured to combat this highly virulent strain.

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 and that the 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. The withdrawal period is zero days.

[1] 50% Egg Infective Dose.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance Live Infectious Bursal Disease virus, strain V877 at $10^{2.2}$-$10^{3.4}$ EID_{50} and excipients include: Sucrose, sodium dihydrogen phosphate, bovine serum albumin fraction V and dipotassium phosphate.

The container system consists of 20 ml Type 1 glass vials with Type 1 rubber stoppers, closed by an aluminium cap. Vials are autoclaved prior to use and stoppers are steam-sterilised before use. Pack sizes are available as 1 x 1000, 1 x 2000, 1 x 5000, 10 x 1000, 10 x 2000 or 10 x 5000 doses. Not all pack sizes may be marketed. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain, inactivating agent and the absence 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.

Specific pathogen free (SPF) eggs are disinfected and then inoculated with working seed virus. After incubation, and verification, embryos are harvested, pooled and stabiliser added. The product may be stored for two years at -30°C, and a sample is tested for microbial count before storage.

In order to obtain the correct titre for the product, several batches of antigen may be mixed. The final bulk being homogenised, and then filtered if necessary. Filling of the vials is performed to ensure a minimum titre of 2.5 $\log_{10}$ EID_{50} and vials then undergo lyophilisation. Batch to batch consistency is checked, and validation studies are provided for microbial count and virus titration.

C. Control of Starting Materials

The active substance is Live Infectious Bursal Disease Virus, strain V877 an established active substance not described in the European Pharmacopoeia (Ph.Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with 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 Guidelines. 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

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 for the bovine serum albumin component. No other data were required.

E. Control tests during production

The tests performed during production are described and the results of five batch to batch consistency tests, conforming to specification, are provided. Other in-process control tests include a visual inspection, a vacuum test, microbial count and virus titre measurement.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements and any deviation from these requirements is justified. The tests include a visual inspection, vacuum test, identity and safety tests, microbial test, avian mycoplasma analysis, extraneous agents tests and residual humidity analysis.

The demonstration of the batch to batch consistency is based on the results of three 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 substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

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

Data were provided from a series of batches of bulk antigen. The product was shown to be stable for twenty-four months at ≤30°C post suspension.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the product as packaged for sale is twenty-one months.
Shelf-life of the product after reconstitution and according to directions - use within four hours.

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 was demonstrated in a series of GLP compliant studies. The investigations were performed according to the recommendations of Directive 2001/82/EC as amended and to the relevant guidelines. Some studies employed the use of the naso-ocular route of administration because dosing via water intake cannot be so readily controlled. The first study analysed the administration of a single, ten-fold dose. A suitable number of specific pathogen free (SPF) chicks, seronegative for IBDV were inoculated orally at a dose rate of 5.5 $\log_{10}$ EID_{50}. Daily clinical observations were performed, and it was noted that there were no adverse reactions to the vaccine. The repeated administration of one dose was also evaluated in this study, and no adverse reactions were noted.

In a second study, bursal damage after administration of the vaccine was observed in a group of chicks exhibiting variable serology for MDA, using a dose rate of 3.3 $\log_{10}$, via the naso-ocular route. Vaccinated birds showed a rise in titre five weeks post vaccination, with bursal weight being similar before and after necropsy. An unvaccinated control group showed a decline in titre. Bursal damage was resolved five weeks post-vaccination, and a higher level of MDA was shown to delay any damage caused by the vaccine. A third, similar study supported the second.

Administration of an overdose was analysed using a further series of studies. The first study assessed the safety of a repeated dose, and data relating to ‘reversion to virulence’ were also provided. A suitable number of birds in two groups were dosed orally at a dose rate of 4.7 $\log_{10}$ EID_{50}. No adverse reactions were noted, and bursal damage was resolved by subsequent regeneration of the organ. Two studies provided data on ten-fold dosing. In the first study, one group received vaccine at a dose rate of 4.5 $\log_{10}$ EID_{50}, the other group received no vaccine. No adverse reactions were noted, and any damage to the bursa in vaccinates was resolved via regeneration.

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

With regard to putative immunosuppression caused by Poulvac Bursa Plus, a further series of studies were performed. A number of SPF chicks were allocated to three groups and inoculated with vaccine at a dose rate of 3.7 $\log_{10}$ EID_{50} via the ocular route. Several days later, the birds were challenged with Newcastle Disease virus (NDV) vaccine. It was noted that there was a lowered response to NDV vaccine where the NDV vaccine was given within seven days of the Poulvac Bursa Plus vaccine. This is highlighted in the SPC. The depletion is due to persistent damage to the bursa, and this is also highlighted in the SPC. A second study analysed the effect of Poulvac Bursa Plus on *Brucella abortus*

vaccination. No adverse effects were noted and there was no effect on the *B. abortus* serological response.

A third study provided data on a comparison between chicks with varying IBD MDA. Here, the purpose of the study was to analyse the influence of anti-IBD MDA on immunosuppression resulting from vaccination with Poulvac Bursa Plus, by assessing the response to NDV vaccine. A suitable number of birds with varying MDA, or no MDA were used in the study, each group was subdivided into two further groups for naso-ocular challenge as necessary. It was shown that vaccination with Poulvac Bursa Plus did not appear to alter the serological response to NDV vaccine. A similar study analysed the response of chicks to Newcastle Disease virus vaccine where the birds had been previously vaccinated with Poulvac Bursa Plus or were unvaccinated. Response to NDV challenge was used to measure results. No adverse reactions were noted, and the SPC carries a specific warning with regard to the use of NDV vaccine in collaboration with the Pulvac Bursa Plus vaccine. Some immunosupression with regard to NDV vaccine was observed.

For the live strain included in the vaccine, specific studies were carried out to investigate the spread, reversion to virulence, recombination or genetic reassortment of the vaccine strain.

Transimissibility

For this study, a large number of chickens were divided into two groups and given either Poulvac Bursa Plus via the oral route at a dose of 3.5 $\log_{10}$ EID_{50}, or left unvaccinated. Lateral spread of the virus was seen to occur, this is highlighted in the SPC.

Reversion to Virulence

No reversion to virulence was noted in two further studies.

Recombination or genetic reassortment of strains

No studies were presented on this subject as it is highly unlikely that a reassortment would occur leading to generation of a virus of greater pathogenicity than those already seen in the field.

Interaction with Other Vaccines

The interaction of the vaccine with NDV vaccine was studied. The interaction noted with NDV vaccine is highlighted in the SPC as follows:-

Interaction with vaccination against Newcastle Disease has been studied. No significant interference in protection against Newcastle Disease virus virulent challenge is observed in birds vaccinated at 10 days of age with Poulvac Bursa Plus and 7 days later with a live Newcastle disease vaccine. However, a statistically lower serological response to Newcastle Disease virus was observed in birds vaccinated with Poulvac Bursa Plus. As a consequence a transient immunodepression following vaccination with Poulvac Bursa Plus cannot be excluded.

No information is available on the compatibility of this vaccine with any other. Therefore the safety and efficacy of this product when used with any other (either used on the same day or at different times) has not been demonstrated.

Field studies

In the first study, a large number of birds on a suitable number of farm premises with a previous history of outbreaks of Gumboro disease were treated with Pulvac Bursa Plus. Two vaccine batches, one comprising a dose rate of 3.7 $\log_{10}$ EID_{50} and the other 3.4 $\log_{10}$ EID_{50} were used to inoculate chicks. No adverse effects were noted and the vaccine was deemed safe for use.

In a second study a large number of birds were inoculated at a variety of sites where Gumboro disease was prevalent. Titres of dose ranged form 3.0-3.3 $\log_{10}$ EID_{50}. No adverse reactions were noted. Results from a third study supported the first two studies.

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 this vaccine is minor.

Warnings and precautions as listed on the product literature and under Special Precautions for use in Animals in the SPC are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

Two pivotal efficacy studies were presented in laboratory trials for Poulvac Bursa Plus. In the first study, a number of chicks were divided into three groups and vaccinated orally with Poulvac Bursa Plus. Group 1 received a dose rate of 1.9 $\log_{10}$ EID_{50}, group 2, 2.2 $\log_{10}$ EID_{50}. The third group was a control. The birds were then challenged with IBD, and subsequently necropsied after nine or ten days. No adverse reactions were noted, the vaccine was efficacious in inoculated birds and bursal scoring was within acceptable levels for vaccinates. The second study mimicked the first, however, this study used chicks with MDA. No adverse reactions were noted, the vaccine was efficacious in inoculated birds and bursal scoring was acceptable for vaccinates.

Studies were also performed to analyse the onset and duration of immunity. Results of these studies supported the claim in the SPC for the onset of immunity taking place fourteen days from vaccination, and the duration of immunity being established as thirty-two days. Further supportive evidence was presented which investigated the compatibility of graded doses of a variety of Poulvac products, no difference was noted.

Field Trials

Four field trial studies were presented. In the first study, Poulvac Bursa Plus was placed in drinking water on a farm harbouring a large number of housed birds. The vaccination dose rate was 1.9 $\log_{10}$ EID_{50} in the first group and 2.2 $\log_{10}$ EID_{50} in the second group. A third group received no vaccine. No unduly adverse reactions were noted in vaccinates. The second study investigated the use of the product on several farms. Two batches were used, the first had a titre of 3.7 $\log_{10}$ EID_{50} and the second a titre of 3.4 $\log_{10}$ EID_{50}. A third group received no vaccine. No unduly adverse reactions were observed in vaccinates. Two further similar studies, also performed in large numbers of birds, supported the results of the first two studies.

Clinical Studies Conclusions

The following conclusions can be drawn from the clinical studies:

Efficacy of the vaccine (minimum titre) has been shown using SPF chickens of the minimum age recommended: reduction of the bursal lesions and prevention of the mortality caused by a vvIBDV was achieved in those animals. An onset and duration of protection of respectively 14 and 32 days have been demonstrated.

Efficacy of the vaccine in the presence of a range of MDA titres (mean titre of around 500 ELISA Units as recommended) was also shown under laboratory conditions: significant reduction of the bursal lesions was shown at 14 and 32 days post challenge. A detailed analysis of the data provided concluded that Poulvac Bursa Plus is able to overcome IBD ELISA titres of ≥500.

Poulvac Bursa Plus has a negative impact on the serological response induced by vaccination against NDV. However, this effect did not affect the ability of the ND vaccine to protect against challenge with virulent NDV. The effect on serology is adequately reflected in the SPC.

Under field conditions that Poulvac Bursa Plus is able to restore performance lost due to vvIBD which has broken through the protection provided by classical vaccines containing mild or intermediate strains. These benefits have been shown in the field in circumstances where the product is intended to be used and in the face of MDA levels which must necessarily be considered typical.

Although no compatibility is claimed, serological data have been provided to support an absence of a negative interaction between Poulvac Bursa Plus and other vaccines.

The benefits of the product have been adequately demonstrated and it was considered that any risks associated with residual virulence is a recognised risk associated with this type of product, which is only recommended for use in an environment contaminated with vvIBD. There are sufficient recommendations and warnings provided to ensure that the veterinarian can determine whether the product is appropriate for use in an outbreak of vvIBD.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)